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EXPERIENCE WITH TOLBUTAMIDE (ORINASE)* IN THE MANAGEMENT OF 100 CASES OF DIABETES

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FOR THE PAST TWO YEARS there has been extensive investigation into the mode of action and the clinical effectiveness of orally administered substances which lower the blood sugar. This field has now become of particular interest to Canadian practitioners since one of these agents, tolbutamide, has recently been released for sale in this country on doctors' prescription.

This chapter in the history of diabetes began in 1942 when Loubatières in France was investigating a new German sulfonamide, isopropylthiodiazole, and noted that it had a blood sugar lowering action in dogs which was related to the sulfanilylamide level in the blood. Janbon and his group, also at Montpellier, in clinical trials of isopropylthiodiazole, encountered a number of severe hypoglycæmic reactions with some fatalities. These reactions resembled those of insulin hypoglycæmia with the exception that they were reversible only with prompt and generous administration of glucose. This hazard of intractable hypoglycæmic reactions discouraged more extensive clinical use of isopropylthiodiazole.

In 1955, a new sulfonamide undergoing tests in Germany proved to have a hypoglycæmic reaction similar to that of isopropylthiodiazole.[1] This drug became known as carbutamide or BZ55 and was subjected to extensive pharmacological study and therapeutic trials in Germany,[2, 3] Britain,[4] Canada,[5] and the United States.[6] American workers encountered a high incidence of toxic reactions[7] which had not been reported in earlier European studies. Some of these reactions were fatal and this led to the drug being withdrawn from further clinical trials in Canada and the United States in October 1956.

However, the advent of carbutamide added a new stimulus to research in the field of diabetes and particularly into the possible mode of action of sulfonylurea compounds in lowering blood sugar levels. There are already extensive and conflicting experimental studies in the literature, and during the Conference on the Effects of the Sulfonylureas and Related Compounds sponsored by the New York Academy of Sciences in February 1957, it was apparent that there was, as yet, no certainty regarding their mode of action.

Generally speaking, they appear to exert little or no effect in the absence of the pancreas, and their ultimate effect on glucose metabolism is probably mediated through endogenous insulin. They do not appear to neutralize insulin antagonists such as glucagon. At the present time, they may be regarded as stimulating existing islet tissue to secrete more insulin. In addition, there is some evidence that carbutamide may inhibit insulinase and thus spare insulin from destruction.[8]

Not long after the introduction of carbutamide, investigation began in Germany on a related compound N-(4-methyl-benzenesulfonyl)-N′-butyl-urea or tolbutamide (D860, Rastinon, Orinase).

We began to use tolbutamide (Orinase) in September 1956, in extension of clinical trials begun earlier with carbutamide, and this report deals with our observations on the first 100 cases treated with tolbutamide.

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MATERIAL AND METHODS

The chief sources of patients employed in these clinical trials were the public metabolism service of the Ottawa Civic Hospital and the private practice and D.V.A. Clinic Service of the senior author. Four cases were under the care of Dr. J. Feller at Rockcliffe R.C.A.F. Hospital and are included with permission of Group Captain J. A. Mahoney, Officer Commanding.

Five of the patients had previously been controlled on carbutamide (BZ55) before the reported toxicity of this drug and the availability of tolbutamide caused a changeover to the latter substance. All patients responsive to carbutamide later proved responsive to tolbutamide (Cases 1, 2, 3, 4 and 5). Case 5 was lost to follow-up and is not included in the tolbutamide series. Case 7 who had indifferent control on BZ55 was later fairly well controlled on tolbutamide. Cases 8 and 9 were carbutamide failures and were not subsequently tried with tolbutamide.

Selection of the earlier cases was from the group most likely to respond to oral antidiabetic agents, that is, the more stable diabetics, not liable either to hypoglycæmia or ketosis, with onset after age 40, and requiring not more than 40 units of insulin daily for control. After the first 20 cases, however, the basis of selection was broadened to include a representation of all age groups (excepting juveniles under 20) and cases of longer duration and with degenerative complications, together with a few cases of diabetes attributed to corticosteroid therapy, pancreatitis and hæmochromatosis. There were 51 females and 49 males in the series and 68 were hospitalized for the initial period of study, the balance being followed either through the out-patient clinic or through the office. The patients ranged in age from 21 to 91 years.

Before the institution of tolbutamide therapy, an attempt was made to determine the optimum dietary and insulin requirements. In all cases in the initial phase of the study and later in most new diabetics and brittle diabetics, a period of control in hospital was undertaken for at least one week before starting the drug. The out-patient group had been regular attenders at the diabetic clinic or were private patients with a sufficiently long and detailed medical record to provide information regarding the quality of control. In general, the established dietary program was continued, but if the diet plan required adjustment or the patient contemplated reform in diet discipline such changes were undertaken in advance of the control period. Furthermore, mild diabetics taking small doses of insulin were first given a trial without insulin for several days before beginning the use of tolbutamide in order to determine if anything beyond a diet program was still required. Some false successes would be obtained and patients needlessly encumbered if this practice were not carried out.

Initial and follow-up laboratory studies consisted of determination of leukocyte count and hæmoglobin, urinalysis, and estimation of fasting and 2½-hour postprandial blood sugar. The urine of each patient was also tested for reducing substances from two to four times daily. Fasting and postprandial blood sugars were determined daily until a stabilized and maintained effect was noted. Thereafter, they were determined as judged necessary, usually at weekly intervals initially and subsequently every two to four weeks.

The initial dose of tolbutamide was given 24 hours after the last injection of modified insulin and it varied from 0.5 to 2 g., the average being about 1 g. The average maintenance dose is indicated in Table III. Where more than 1.5 g. per day was required, it was the usual practice to divide the dose between breakfast and lunch or breakfast and supper. Other indications for dividing the dose are gastric irritation from ingestion of a single large dose of tolbutamide or difficulty in obtaining a satisfactory fasting blood sugar.

CRITERIA

The efficacy of any technique for obtaining control of diabetes must be interpreted in relation to criteria defining successful control. It is obvious that with less stringent criteria, there will be a higher rate of "success". Certain factors relating to this point merit further discussion.

It is generally agreed that ideal control means that the blood sugar levels of a diabetic conform to the diurnal curves of a normal individual, that is, a fasting blood sugar of 80-120 mg. % (using a "total reducing substance" method) and postprandial peaks which do not rise above 170 mg. % and which return to the normal fasting range within 2½ hours of the midpoint of the meal. Ideal control and excellent control may be regarded as practically synonymous.

Good control may be said to exist when the blood sugar is usually normoglycæmic. Occasional fasting and 2½-hour postprandial blood sugars may range up to 150 mg. % with occasional mild glycosuria. Hypoglycæmic reactions should be rare.

With fair control the fasting and 2½-hour postprandial blood sugars should be under 200 mg. % and occasional moderate glycosuria exists.

Poor control or failure is characterized by blood sugars usually over 200 mg. % and moderate to heavy glycosuria.

Qualified success might reasonably be claimed in a small proportion of cases where the tolbutamide regimen was less satisfactory than insulin, provided it was not more than one category worse and not less than fair. This group would include persons who could be self-sufficient on a tolbutamide program but were dependent on others for insulin administration because of poor vision from cataracts or retinopathy, limited dexterity from neurologic or arthritic disorders, or limited intelligence or education; those who stubbornly refuse to use insulin for religious or other reasons; those who prove less liable to frequent and severe hypoglycæmic reactions on tolbutamide, and those with insulin fat atrophy or insulin allergy.

RESULTS

Of the 100 cases in the group, 60% were regarded as successfully controlled and 40% failed to respond adequately to tolbutamide. Two of those classified as successful in so far as blood sugar control was concerned were later forced to discontinue tolbutamide because of the development of side effects.

About 65% of female diabetics responded to tolbutamide, as compared to 55% of males.

The average follow-up period was 17 weeks with a range of from 8 to 41 weeks. With longer follow-up it is probable that some of the successes will fail to be maintained in satisfactory control, either because of an inherent tendency for diabetes to be more difficult to control the longer it exists, or because of the more immediate problem of weight gain from a too casual dietary regimen. This tendency to gain weight while using tolbutamide was noted in a considerable number of patients and may, in part, be attributed to the fact that most patients controlled on tolbutamide enjoyed a better quality of control with less glycosuria than had been obtained with insulin (Tables I, II and III). The factor of greatest importance in causing weight gain is probably a more casual approach to the whole regimen which is engendered by the apparent simplicity of taking tolbutamide.

TABLE I.

COMPARISON OF QUALITY OF CONTROL ON INSULIN REGIMEN VS. TOLBUTAMIDE

Control rating	*On insulin*	*On tolbutamide*
	cases	*cases*
Excellent	4	17
Good	17	24
Fair	39	19
Poor	40	40
Total	100	100

Table I compares the quality of control on tolbutamide as opposed to the previous insulin program. It is seen that only 4% of the 100 patients were classified as in excellent control on insulin whereas 17, including these 4, were in excellent control with tolbutamide. Seventeen had good control with insulin and 24 with tolbutamide. There were 39 patients in only fair control on insulin and 19 in fair control on tolbutamide; 40 were poorly controlled on insulin and the same number, but not the same patients, were in poor control on tolbutamide.

TABLE II.—SUMMARY OF CHANGES IN CONTROL RATING OF CASES SUCCESSFULLY CONTROLLED ON TOLBUTAMIDE

1. Cases worse by one category	5
2. Cases worse by two or more categories	0
3. Cases unchanged in category	17
4. Cases better by one category	20
5. Cases better by two or more categories	18

Table II summarizes the changes in control rating of the 60 cases successfully controlled on tolbutamide; 17 were unchanged with respect to quality of control, 20 were better by one category, 18 by two or more categories, and only five were less well controlled and none of these by more than one category. This number is small because, in general, poorer control would not be regarded as satisfactory. Such cases would fall into the group of qualified successes as defined above, where slightly poorer control might be tolerated for other reasons (usually environmental).

Table III summarizes clinical data on each of the 60 successfully controlled patients, and Table IV gives similar information regarding those who failed to respond adequately to tolbutamide therapy. These tables are supplemented by brief protocols on illustrative cases.

TABLE III.

Case No.	Patient	In-Patient	Out-Patient	Sex	Age	Body build	Before tolbutamide: Years since diagnosis	Before tolbutamide: Average daily insulin	Before tolbutamide: Cont. rating	On tolbutamide: Average daily dose (g.)	On tolbutamide: Follow-up (weeks)	On tolbutamide: Cont. rating	Remarks
1	A.W.	In	—	F	70	M	4	25	G	1	41	F	Initially on carbutamide, 1 g.
2	E.M.	In	—	F	70	M	5/12	30	G	1	41	F	Initially on carbutamide, 1 g., gained weight.
3	J.R.	In	—	F	59	H	12	0	G	1	39	G	Initially on carbutamide, 1 g., gained weight.
4	G.K.	In	—	M	39	M	New	0	P	1	27	E	New diabetic with sugar over 400 mg.%—see protocol.
7	W.H.	—	Out	M	46	M	1/12	0	G	1	12	G	Control poor on carbutamide 1.5 g. and reverted to insul. then tolbutamide.
10	L.F.	In	—	F	75	S	1/12	25	P	1.5	25	F	Senility an indication for oral therapy.
11	E.P.	In	—	F	63	M	3	15	F	1.5	14	F	'Steroid' diabetes in arthritic on cortisone. Had stomatitis on carbutamide.
16	L.L.	In	—	M	67	M	2/12	15	F	1.0	26	G	.....
20	A.D.	In	—	M	57	H	4	35	F	1.5	29	F	.....
21	C.R.	In	—	M	77	S	1	16	E	1.0	27	G	Senility; poor vision. Diabetic neuropathy with ataxia.
25	S.T.	In	—	M	72	S	10	38	F	2.0	25	F	Chinese, asthmatic and brittle diabetic, much improved on tolbutamide.
27	N.W.	In	—	M	86	S	15 plus	60	P	2.0	3	F	Fatal hypoglycæmic coma.
28	A.V.	—	Out	F	65	S	5	20	G	0.5	10	E	.....
30	W.S.	In	—	M	47	H	1/12	18	G	1.0-0	24	E	New diabetic.
31	M.F.	In	—	F	91	M	8	30	F	1.5	25	G	Senility prevented her from managing insulin regimen.
32	W.S.	—	Out	M	46	M	8	25	F	1.5	20	G	Psychopath and alcoholic; tolbutamide control simpler and better, even in jail.
33	G.C.	In	—	F	73	M	5	75 plus	E	1.5	20	G	Arteriosclerotic heart disease with heart block and decompensation.
34	C.D.	—	Out	M	80	H	4	40	6	2.5	15	G	Local swellings and urticaria from insulin.
35	L.P.	—	Out	M	55	M	8/12	25	F	1.5	3	F	Developed focal seizures after 3 weeks on tolbutamide, resumed insulin.
36	M.F.	In	—	F	54	M	20	35	P	1.5	20	G	Psychopath, poverty and neglect; repeated infections of feet.
38	C.C.	In	—	F	64	H	5	40	F	1.5	21	F	Hemiparesis prevented self-administration of insulin.
40	L.L.	In	—	F	40	H	9	50	F	1.0	21	E	Carried through operation for endometriosis.
41	M.B.	In	—	F	70	S	2	0	G	1.0	18	G	Depression and senility.
43	B.M.	In	—	F	63	M	1	15	F	0.5	19	G	'Steroid' diabetes in arthritis on cortisone.
44	B.W.	—	Out	M	78	S	11	70	F	1.5	20	F	Well preserved for age. Delayed response to tolbutamide.
49	M.H.	In	—	F	75	M	20	25	G	1.0	22	G	Elderly woman with arteriosclerotic heart disease and decompensation.
51	M.C.	In	—	F	63	H	14	0	P	1.5	17	F	Obese with peripheral neuropathy; refused to take insulin.
56	H.M.	In	—	M	76	M	New	0	F	1.5	14	E	Crusty old man who refused insulin. Carried through T.U.R.
57	D.R.	In	—	F	69	H	2	30	F	2.0	17	F	Tolbutamide started after operation for large non-toxic goitre.
62	E.D.	In	—	F	29	M	4	10	E	1.5	14	E	Delayed excellent response in juvenile diabetic.
65	E.M.	—	Out	F	54	M	13	0	F	1.5	13	G	Refused insulin after tolbutamide available.
66	F.B.	—	Out	F	36	M	1	15	F	1.5	15	F	Delayed response.
67	M.C.	In	—	F	67	M	4	80	F	2.0	9	F	Nausea and vomiting when tolbutamide first used.
69	W.P.	In	—	M	62	M	New	22	F	1.5	12	F	Although control only fair he refused to resume insulin.
70	L.L.	In	—	F	73	M	4	0	P	1.0	13	F	Also has rheumatoid arthritis.
71	A.W.	In	—	F	75	M	New	0	P	1.5	12	G	Vision limited by cataracts.
72	J.L.	In	—	M	43	H	13	20	P	3.0	12	F	Poor diet discipline.
73	M.D.	In	—	F	54	M	5	10	E	1.0	12	E	Dwarf of uncertain type.
74	A.L.	In	—	F	69	M	5	56	F	1.5	11	F	.....
75	G.L.	In	—	M	57	H	New	15	F	1.0	11	E	.....
76	A.L.	In	—	F	67	M	1	18	F	1.5	12	E	Tolbutamide started after cholecystectomy.
77	A.W.	—	Out	F	66	M	3	20	P	1.0	16	G	Moderate retinopathy.
78	G.S.	—	Out	F	75	H	10 plus	100	P	2.0	13	F	Obese. Poor diet discipline.
79	H.J.	—	Out	F	58	M	6/12	0	P	2.0	13	G	Poor co-operation. Had stopped insulin without authority.
80	S.S.	—	Out	M	76	S	15	35	F	1.5	16	G	.....
81	M.C.	—	Out	F	58	M	20	10	G	1.5	13	E	Prone to urticaria with insulin
82	R.O.	—	Out	M	55	S	12	35	F	3.0	18	G	Obese; dose divided in 3 parts eliminating gastric irritation.
85	M.H.	—	Out	M	76	H	New	0	P	1.0	11	G	Infected foot healed on tolbutamide regimen.
86	H.M.	—	Out	M	66	H	10	0	P	2.0	16	G	Bon vivant who resisted insulin.
87	M.H.	—	Out	F	75	S	10	35	G	1.0	21	E	Poor vision made her dependent on others for insulin.
89	H.S.	—	Out	M	48	H	8	20	F	1.5	16	E	.....
90	S.B.	In	—	F	68	S	6/12	60	F	1.0	10	G	Diabetes developed after severe pancreatitis.

TABLE III.—*Continued*

Case No.	Patient	In-Patient	Out-Patient	Sex	Age	Body build	Before tolbutamide: Years since diagnosis	Before tolbutamide: Average daily insulin	Before tolbutamide: Cont. rating	On tolbutamide: Average daily dose (g.)	On tolbutamide: Follow-up (weeks)	On tolbutamide: Cont. rating	Remarks
92	O.M.	—	Out	M	60	M	10	0	P	1.0	10	G	Hospital orderly on shift work.
93	J.O.	—	Out	M	60	M	4	10	F	1.0	10	E	Moderate diabetic neuropathy.
99	T.M.	—	Out	M	40	M	15	10	G	1.5	11	E	.....
101	W.H.	In	—	M	69	M	23	39	G	0.5	8	F	.....
102	A.H.	—	Out	F	61	M	3	0	P	1.5	10	E	.....
104	M.M.	—	Out	F	72	M	4/12	21	F	0.5	11	G	.....
106	H.M.	In	—	M	28	H	New	20	P	1.5	9	G	R.C.A.F. hospital case
108	M.M.	—	Out	M	53	M	4	0	F	1.5	19	E	Dizzy with starting dose of 2.5 g.

Body build:
S—Slender
M—Medium
H—Heavy

Control rating:
E—Excellent
G—Good
F—Fair
P—Poor

FACTORS INFLUENCING RESPONSE TO TOLBUTAMIDE

Sex.—It has already been noted that female diabetics were somewhat better controlled on tolbutamide than were males.

Age at onset of diabetes.—Fig. 1 shows that age at onset is a significant factor in predicting the probability of response. It is seen that in the 40 to 80 age group, there is a better than average chance of obtaining satisfactory control on tolbutamide, whereas outside of these age limits there is a diminished likelihood of success.

TABLE IV.

Case No.	Patient	In-patient	Out-patient	Sex	Age	Body build	Before tolbutamide: Years since diagnosis	Before tolbutamide: Average daily insulin	Before tolbutamide: Control rating	Tolbutamide Average daily dose (g.)	Remarks
12	C.W.	In	—	M	30	M	10	75	F	1.5	Low intelligence and poor motivation.
13	J.M.	In	—	F	21	M	16	25	P	1.5	Reaction 3 PM on ½ insulin plus tolbutamide; thereafter more brittle.
14	P.H.	In	—	M	58	M	8/12	20	6	1.5	Partial response, but vague malaise caused by tolbutamide.
15	H.H.	In	—	M	58	H	4	32	F	1.5	.....
17	S.B.	In	—	F	74	M	12	26	P	1.5	.....
18	D.G.	In	—	F	47	M	3	42	F	1.5	Developed severe ketoacidosis during tolbutamide trial in hosp.
19	C.M.	In	—	M	82	S	4	16	P	1.5	Senile.
22	J.H.	In	—	M	72	M	6	0	P	1.5	.....
23	C.P.	In	—	M	60	S	New	30	P	2.0	Atrophic cirrhosis as well as diabetes.
24	R.P.	In	—	M	75	M	New	0	P	2.0	Developed flushing and nausea on tolbutamide; bronchiectasis.
26	H.G.	In	—	F	80	H	21	105	P	2.0	Sjögren's syndrome?
29	V.B.	In	—	F	57	H	25	90	P	1.5	Advanced retinopathy; developed diarrhœa on tolbutamide.
37	S.W.	In	—	F	79	S	11	15	P	1.5	Cataracts.
39	W.L.	In	—	M	79	S	1/12	35	P	1.5	.....
42	K.B.	In	—	F	65	S	6	30	P	2.0	Severe ketoacidosis within 24 hours of stopping insulin.
45	J.S.	In	—	M	43	M	12	28	F	1.5	.....
46	M.S.	In	—	F	58	M	5	50	P	1.5	Allergy to protamine; later stabilized on lente.
47	M.C.	—	Out	F	69	H	20	120	F	2.0	Insulin resistant hemiplegia.
48	M.M.	In	—	F	73	S	7	300 plus	P	1.5	Insulin resistant diabetic.
50	M.C.	In	—	F	66	H	3	15	P	1.5	Asthma, hypertension, cardiac decompensation.
52	F.B.	In	—	M	80	M	1	30	F	1.5	Pemphigus made injections undesirable.
53	J.Z.	In	—	F	76	H	15	80	F	1.5	.....
54	L.C.	In	—	M	58	S	4	100	P	2.0	Hæmochromatosis; brittle diabetes.
55	E.M.	In	—	M	63	M	12	75	P	3.0	Brittle and unco-operative psychopath; foot ulcers.
58	R.C.	In	—	M	51	M	6	70	P	2.0	Hæmochromatosis.
59	L.V.	In	—	M	39	H	6	30	P	1.5	.....
60	E.C.	In	—	F	66	M	10	20	F	1.5	Bl. sugar rapidly rose to over 400 mg. on tolbutamide.
61	N.S.	In	—	M	64	M	4	95	P	2.0	.....
63	N.M.	In	—	F	74	M	20	28	F	1.5	.....
64	S.A.	—	Out	F	61	M	32	40	F	1.5	.....
83	L.S.	—	Out	F	47	M	5	25	G	2.0	Unexpected failure of tolbutamide.
84	W.C.	—	Out	M	60	S	3/12	0	P	2.0	.....
88	G.D.	—	Out	F	45	M	17	34	F	2.0	.....
91	C.P.	—	Out	F	78	M	6	25	G	1.5	Ketoacidosis developed on outpatient trial of tolbutamide, admitted.
94	F.L.	In	—	M	70	S	10	0	P	1.5	Advanced retinopathy.
95	J.N.	In	—	M	75	M	7	130	P	1.5	.....
97	S.W.	—	Out	M	64	M	10	26	G	2.0	.....
100	T.G.	In	—	F	61	M	12	25	P	2.0	.....
105	A.H.	—	Out	M	62	M	30	18	F	1.0	Advanced diabetic nephropathy.
107	A.B.	In	—	M	47	M	3	80	P	1.5	.....

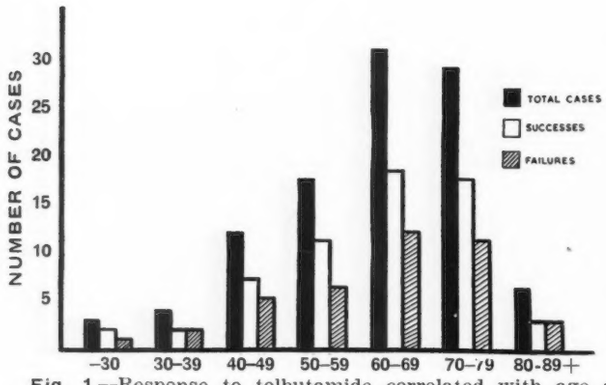

Fig. 1.—Response to tolbutamide correlated with age at onset of diabetes.

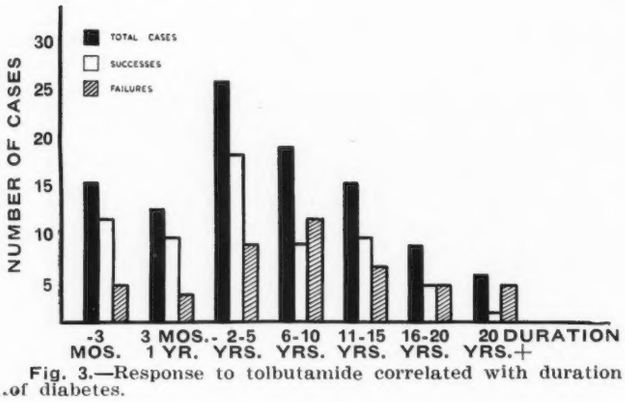

Fig. 3.—Response to tolbutamide correlated with duration of diabetes.

Body build.—Fig. 2 indicates that diabetics of average or heavy build are more likely to respond to tolbutamide than thin patients. This observation has been made by most authors and it probably reflects the fact that obese diabetics tend to have a milder disorder than those who are lean. This factor may also have weighted the success rate in females, where there is a somewhat greater tendency to obesity.

Duration of diabetes.—The importance of this factor is indicated in Fig. 3, which shows a preponderance of successful responses to tolbutamide in patients with diabetes of less than five years' duration, about an equal number of successes and failures in the group with diabetes from 5 to 20 years, and a poorer response in those whose disease is greater than 20 years in duration.

The former insulin requirements.—Fig. 4 indicates that insulin requirements are related to the probability of success with tolbutamide. With a daily insulin requirement of less than 25 units, the success rate is at least twice as great as the rate of failure. Between 25 and 75 units per day, there is about an even chance of obtaining a satisfactory response with tolbutamide, and in those requiring larger doses of insulin, few successes are anticipated.

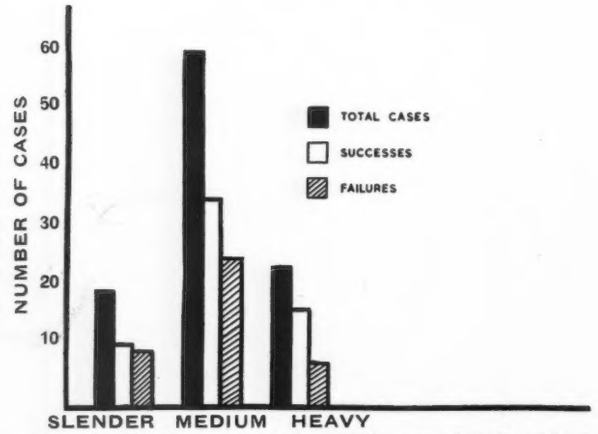

Fig. 2.—Response to tolbutamide correlated with body build.

Side Effects and Reactions Attributed to Tolbutamide

Undesirable effects from the use of oral antidiabetic agents might be divided into three groups:

1. *Side Effects*—With tolbutamide, the most common true side effect was related to gastrointestinal irritation. A sense of epigastric distress and fullness was reported by four of our group. This symptom was usually associated with doses in excess of 1 g. and could be controlled by dividing the dose into 1 g. fractions. One patient had nausea and vomiting with initiation of tolbutamide treatment and reverted to insulin for a time. However, she was later able to tolerate tolbutamide. Another patient (Case 11) who had a steroid diabetes due to cortisone treatment of rheumatoid arthritis was forced to discontinue tolbutamide when nausea and vomiting supervened after about six weeks of treatment. Two further trials of tolbutamide were carried

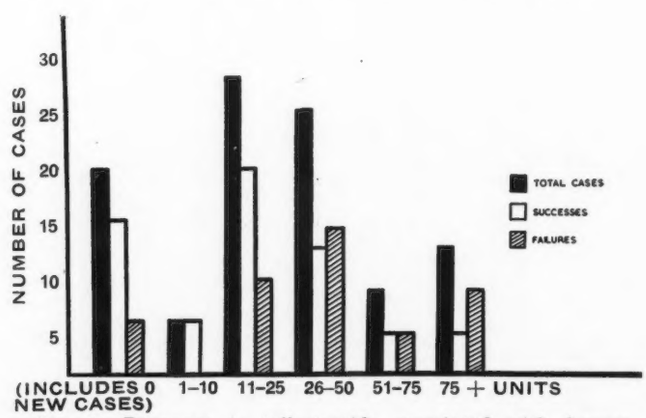

Fig. 4.—Response to tolbutamide correlated with former insulin requirement.

out subsequently with recurrence of nausea and vomiting on each occasion. This woman had previously developed stomatitis on carbutamide which cleared when that drug was discontinued. One patient who had a long-standing diabetes with severe degenerative complications developed diarrhœa with the institution of tolbutamide therapy and she failed to respond with respect to blood sugar.

General malaise of a vague type was reported by two patients, and in one man (Case 14) tolbutamide was discontinued after several weeks because of this symptom, although he had responded as regards control of blood sugar.

A skin eruption of a fine vesicular nature developed during a trial of tolbutamide in an elderly insulin-resistant woman who previously had encountered difficulty with urticaria when insulin therapy was instituted. She also failed to respond to tolbutamide with regard to blood sugar control.

2. *Overdosage Effects*—These are comparable to insulin reactions and are due to hypoglycæmia caused by an unexpected sensitivity to the dose of tolbutamide employed. Apart from individual differences in response to any drug, it is important to keep in mind that, through its reported anti-insulinase action, tolbutamide may potentiate the remaining portion of a dose of long-acting insulin taken the previous morning. This was the probable explanation for a hypoglycæmic reaction occurring within a few hours of the initial dose of tolbutamide in two of our patients who subsequently failed to respond to tolbutamide alone. They might have responded well to tolbutamide plus a small amount of injected insulin but, as a general principle, it was not thought wise to try to maintain patients on two forms of diabetic therapy where one would suffice. Such initial transient responsiveness could alternatively be attributed to a discharge of stored insulin from islet cells with a failure to replenish it at a comparable rate.

One of our patients, after three weeks of satisfactory control on tolbutamide, developed severe hypoglycæmia and died. This case has previously been reported but a brief protocol accompanies this paper (Case 27).

3. *Loss of control of the diabetic state*—Loss of control of diabetes due to an unsuccessful trial of tolbutamide might be regarded as an indirect effect of the use of the drug. In Cases 41 and 42, two of our in-hospital patients given 1.5 and 2 g. of tolbutamide respectively, developed severe ketoacidosis within 36 and 48 hours of their last dose of insulin. They required vigorous treatment with insulin and saline to retrieve the situation. In all other cases failing to respond, lesser degrees of uncontrol are induced so that it must be stressed that a trial of tolbutamide in any patient taking insulin can never become a casual matter.

Clinical Employment of Oral Antidiabetic Agents

Arising out of a somewhat limited but rather eventful experience with tolbutamide, we have formulated certain principles for the clinical employment of this agent:

Tolbutamide should not be used in treatment of diabetes which has begun before age 20.

Tolbutamide should not be used in attempting to control diabetes in the face of a severe local or general infection.

Tolbutamide should not be used in diabetes which can be controlled by diet.

Tolbutamide should not be used in milder diabetics using small doses of insulin until it has been established by withdrawal of insulin that either insulin or tolbutamide is still required.

Tolbutamide should not be given to emaciated patients or those with a chronically poor intake of food, since such persons seem prone to severe hypoglycæmic reactions. Malnutrition was a feature of the case of fatal hypoglycæmia mentioned earlier and in other severe, but not fatal, cases of hypoglycæmia which have come to our notice.[10]

We fail to appreciate the rationale for initiating treatment with a high dose of tolbutamide (3 g.) and thereafter reducing to the smallest dose needed to maintain control. It would seem safer to start with a lower dose (1 or 1.5 g.) and increase as indicated and usually not beyond a maintenance dose of 2 g. per day. We have regarded as failures those cases in which control was not achieved on 2 g. or less per day.

The brittleness of diabetes in a patient and his proneness to ketosis are not necessarily related to insulin requirements, so that exceptions will be encountered to any rule of thumb which may be offered for safely converting patients from insulin to tolbutamide.

In general, however, where the insulin requirement is less than 20 units per day, it is safe to stop insulin entirely and institute tolbutamide in the dose of 1 or 1.5 g. the first day.

Usually 1 g. is given before breakfast, and if the urine test before supper shows glycosuria, a further 0.5 g. dose is given before supper. If both glycosuria and ketonuria have appeared by the suppertime test, this second dose of tolbutamide may still be given but there is particular need for vigilance regarding further intensification of the ketonuria. One of our more recent cases (not included in this series) developed severe ketoacidosis, although his daily insulin requirement was only 18 units.

In patients with higher insulin requirements, even greater vigilance is needed with respect to development of ketoacidosis. In general, it is safe to gradually withdraw insulin at the rate of a quarter or a half of the total dosage on the first day and similar reductions on subsequent days while tolbutamide dosage is being increased. Where the total daily dose has been greater than 50 units, this gradual withdrawal of insulin is mandatory.

SUMMARY

Experience with tolbutamide treatment of 100 diabetics selected more or less at random from office, clinic and hospital practice is presented. Sixty per cent were satisfactorily controlled with regard to blood sugar levels, using rather strict criteria for control. Side effects were few in number but one death occurred due to intractable hypoglycæmic coma in an elderly malnourished man. Partly as a result of this experience, a cautious approach to the use of high doses of tolbutamide is advocated. It is thought advisable to start with smaller doses of the drug and increase if necessary, rather than to begin with a large dose and decrease.

PROTOCOLS

The following protocols concern a few of the more interesting and illustrative cases.

CASE 4.— G.K., male, aged 40. Diabetes was diagnosed in August 1956, at which time the blood sugar was over 400 mg. %, and the patient was slightly overweight. On a 1400 calorie diet and 1 g. of carbutamide daily the diabetes came under control. In November carbutamide was replaced by tolbutamide 1 g. daily, which could soon be reduced to 0.5 g. per day when a blood sugar of 50 mg. % was obtained 2½ hours after one of the morning doses. Tolbutamide was withdrawn in the latter part of December, but within a month the postprandial blood sugar had risen to 160 mg. %. The patient was permitted to continue without tolbutamide for about three months, but when the blood sugar four hours after lunch was as high as 180 mg. % it was thought best to reinstitute tolbutamide in a dose of 0.5 g. daily. Excellent control was again obtained.

CASE 7.—W.H., male, aged 46. First admitted to Ottawa Civic Hospital in July 1956 with myocardial infarction. Diabetes was diagnosed incidentally and controlled on 16 units of protamine insulin daily. A trial of carbutamide was carried out after the patient had recovered from the infarction. He failed, however, to respond satisfactorily and was discharged to be followed up in the out-patient clinic. Here a trial of tolbutamide was carried out in March 1957, and on 1.5 g. daily he has obtained good control.

CASE 11.—E.P., female, aged 63, with a complicated medical history including severe hypertension for which sympathectomy was done about eight years ago. Thereafter she developed angina, and then a myocardial infarction and congestive failure. Acute rheumatoid arthritis began about three years previously and was unusually severe and rapid in progression considering her age at onset. Initially she received gold therapy, later supplemented by cortisone 25 to 50 mg. per day. Occasionally 75 mg. per day would be used. Nine months after cortisone was started, diabetes developed, and, in general, insulin requirements have paralleled changes in the dose of cortisone. Control was achieved with carbutamide about one year ago but a few weeks after starting this drug she developed an ulcerative stomatitis which led to discontinuing the drug. She resumed taking 15 units of insulin daily until March 1957, when she was again hospitalized for a flare-up of the arthritis. During this admission she was stabilized on 1.5 g. of tolbutamide, which provided good control. The orally administered drug was particularly appreciated by this patient, who was no longer able to administer insulin to herself, but unfortunately a vague sense of nausea and epigastric distress resulted from tolbutamide and finally forced its discontinuation.

CASE 18.—D.G., female, aged 47. This woman with diabetes of three years' duration, taking 24 units of regular insulin and 18 units of protamine insulin daily, was admitted to Ottawa Civic Hospital in November 1956 for a trial of tolbutamide. Insulin was gradually withdrawn and 2 g. of tolbutamide given each morning, but there was increasing glycosuria and ketonuria, and a severe degree of ketoacidosis developed with a blood sugar of 516 mg. % and a CO_2 combining power of 16 vol. %. She responded well to the usual measures for treatment of diabetic coma. This case is of particular interest since it represents a patient in whom one would not suspect undue risk of rapidly developing ketosis since she obtained good control with apparent ease on insulin and diet.

CASE 27.—N.W., male, aged 86. This case concerns a fatal hypoglycæmic reaction in a thin elderly man with diabetes of over 15 years' duration. He

was hospitalized because of pneumonia and ketoacidosis, which was partly attributable to the fact that he had stopped insulin without authorization. Admission blood sugar was 540 mg. % and CO_2 combining power was 38.5 vol. %. The diabetic acidosis and pneumonia responded promptly to treatment, and at the end of 10 days the diabetes had been stabilized by unmodified insulin 40 units and protamine insulin 20 units each morning. Appetite continued poor in spite of all efforts to improve it and he failed to take all of the 1200 calorie diet prescribed.

On the 16th hospital day insulin was reduced by half and 2 g. of tolbutamide was given. There was a prompt fall in blood sugar to 47 mg. % at 2½ hours after breakfast but no symptoms developed. Thereafter the dose of tolbutamide was maintained at 1.5 g. each morning and after the third day insulin was discontinued entirely. At the end of the first week the fasting blood sugar was 153 mg. % and blood sugar 2½ hours after breakfast was 215 mg. %. In an attempt to obtain better control, the tolbutamide was then increased to 2 g. daily and the next day the values were 109 mg. % before and 122 mg. % after breakfast. Two days later, on the same regimen, values were 128 mg. % and 205 mg. % and on the next day 171 mg. % and 201 mg. %. On the 28th day blood sugar levels of 116 mg. % and 148 mg. % were obtained and on the 33rd hospital day the patient was discharged home to continue taking 1 g. of tolbutamide twice daily.

Six days later he was admitted to another hospital in a stuporous condition but revived spontaneously over the next 18 hours so that by the following evening he was able to eat some supper and was given his usual dose of 1 g. of tolbutamide. A few hours later he lapsed into unconsciousness. The nature of the coma remained obscure until the following morning, about 16 hours later, when a blood sugar of 26 mg. % was obtained. In spite of the use of concentrated glucose solution intravenously followed by a continuous intravenous drip of glucose sufficient to maintain moderate glycosuria, he did not regain consciousness. No signs developed to suggest focal cerebral damage. On the fourth day of unconsciousness he roused slightly and made attempts to swallow small amounts of fluid placed in his mouth. By the morning of the fifth day of coma he was noticed to have a generalized measles-like eruption, and he died about noon on that day. At no time was there any appreciable elevation of temperature and the eruption was regarded clinically as possibly representing skin sensitivity to tolbutamide.

Although permission for autopsy was not obtained, it would appear that death was attributable to the effects of prolonged hypoglycæmia on the central nervous system of an elderly patient who probably had considerable cerebral arteriosclerosis.

CASE 30.—W.S., male, aged 46. This newly diagnosed diabetic presented with furuncles and a blood sugar of 230 mg. %. He was stabilized in hospital on 18 units of N.P.H. daily and when the infection was under control this was changed to 1 g. of tolbutamide daily with excellent control. At the end of three weeks the tolbutamide was further reduced to 0.5 g. per day and finally about two months after starting tolbutamide the drug was withdrawn and he has continued in excellent control since, in spite of the fact that there was no change in body weight. This case is of particular interest since it suggests that the action of tolbutamide does not tend to deplete pancreatic reserve. The total follow-up on this patient is over six months, and although he has failed to lose any weight the blood sugar now continues in a strictly normal range.

CASE 35.—L.P., male, aged 55. This man was first seen in early February 1957, with an eight-month history of diabetes which was poorly controlled on 25 units of N.P.H. and a rather free diet. With slight increases in insulin and a more strict diet program, fairly good control was obtained and he was then changed to 1.5 g. of tolbutamide daily and continued in excellent control. About two months after the institution of tolbutamide therapy he was admitted in a coma which was at first thought to be hypoglycæmic, but he failed to rouse after the administration of intravenous glucose, and furthermore the blood sugar taken at that time indicated a level of 160 mg. %. The family stated that he had two similar episodes of unexplained coma within the past year; the neurosurgical service considered the likelihood of brain tumour sufficiently strong to warrant exploration and ventriculography. He had been converted back to an insulin regimen during this admission because of uncertainty of oral intake. In the postoperative period he developed staphylococcal pneumonia and died. Neither the neurological symptoms nor his subsequent death were regarded as related to the use of tolbutamide.

CASE 42.—K.B., female, aged 65. A lean woman with brittle diabetes of six years' duration taking 30 units of insulin daily but with poor control. In December 1956, she was admitted to hospital for a trial of tolbutamide. After a control period of one week insulin was discontinued altogether and 2 g. of tolbutamide given. The blood sugar rose rapidly to 444 mg. % and ketoacidosis developed with a CO_2 combining power of 18 vol. % within 24 hours of stopping insulin. The diabetic coma responded well to insulin and saline, but this case illustrates how rapidly dangerous ketoacidosis may develop following withdrawal of insulin in severe diabetes.

CASE 43.—B.M., female, aged 63. This woman had developed diabetes with classical symptoms of onset about three years previously, after a year of cortisone therapy for subacute rheumatoid arthritis. The dose of cortisone used had averaged about 50 mg. daily and her average insulin requirement was 15 units per day. However, control usually was no better than fair. In the absence of a family history and because diabetes developed during the use of cortisone, it had been regarded as a steroid diabetes. Rather surprisingly she proved unusually sensitive to tolbutamide and was controlled on a maintenance dose of

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0.5 g. per day. Occasionally tolbutamide had to be increased to 1 g. or even 1.5 g. daily, when the amount of cortisone taken was increased in order to control an exacerbation of joint symptoms.

CASE 58.—R.C., male, aged 51. This patient had hæmochromatosis with diabetes of six years' standing, and was taking 70 units of insulin daily with rather poor control of blood sugar levels. He was admitted to Ottawa Civic Hospital in February 1957, and insulin gradually decreased as tolbutamide was introduced. When insulin had been discontinued completely, blood sugar rose rapidly to 460 mg. %. The insulin was then restarted and fair control obtained on 40 units of regular and 30 units of protamine insulin daily.

CASE 90.—S.B., female, aged 68. This woman was admitted to Ottawa Civic Hospital in August 1956 with acute pancreatitis and a history of chronic cholecystitis with cholelithiasis. She was not known to have had diabetes before the attack of pancreatitis and therefore was regarded as having post-pancreatitis diabetes. The diabetes was controlled on 60 units of insulin daily. In October she had a cholecystectomy and common bile duct drainage and was discharged on 40 units of unmodified and 20 units of protamine insulin daily. She was followed up through the out-patient clinic and later readmitted in March 1957 for trial of tolbutamide. She had an immediate response and continued in good control on 1 g. daily.

REFERENCES

1. FRANKE, H. AND FUCHS, J.: *Deutsche med. Wchnschr.*, 80: 1449, 1955.
2. ACHELIS, J. D. AND HARDBECK, K.: *Ibid.*, 80: 1452, 1955.
3. BERTRAM, F., BENDFELDT, E. AND OTTO, H.: *Ibid.*, 80: 1455, 1955.
4. *Brit. M. J.*, 2: August 25, 1956.
5. *Canad. M. A. J.*, 74: 957-98, 1956.
6. KIRTLEY, W. R. *et al.*: *Diabetes*, 5: 351, 1956.
7. *Idem*: *Ibid.*, 6: 72, 1957.
8. MIRSKY, I. A., PERISUTTI, G. AND DIENGOTT, D.: *Metabolism*, 5: 156, 1956.
9. McKENDRY, J. B. R.: *Canad. M. A. J.*, 76: 572, 1957.
10. KARK, R. M.: Personal communication.

RÉSUMÉ

Depuis les travaux de Loubatières sur les sulfamidés à action hypoglycémique, des recherches se sont poursuivies tant en Europe qu'en Amérique si bien que nous avons maintenant à notre disposition au Canada un autre de ces produits, le tolbutamide. Ce médicament administré par voie orale semble augmenter la sécrétion d'insuline en stimulant les îlots de Langerhans. Les auteurs du présent article font part de leurs résultats dans le traitement par cette méthode de 100 diabétiques. Les 20 premiers cas furent judicieusement choisis d'après les raisons qui permettaient d'espérer les meilleurs effets alors que les autres furent pris plus ou moins au hasard. Les résultats obtenus furent qualifiés d'excellents si la courbe du glucose sanguin se conformait à la normale, et furent considérés comme des échecs si la glycémie dépassait 200 mg. pour cent, avec glycosurie fréquente. Soixante de ces malades furent contrôlés avec succès mais deux d'entre eux durent abandonner le traitement à cause des effets secondaires. Tous furent suivis pendant une moyenne de 17 semaines. On observa une tendance à gagner de l'embonpoint que l'on attribua indirectement au traitement vu le relâchement de plusiers malades à l'égard de leur régime alimentaire. Les tableaux inclus dans le texte comparent les résultats obtenus avec le traitment à l'insuline d'une part et au tolbutamide d'autre part. On peut en tirer les conclusions suivantes: *grosso modo* le tolbutamide donnerait un meilleur contrôle que l'insuline; les femmes en général répondent mieux au traitement que les hommes; les obèses obtiennent de meilleurs résultats que les maigres. L'âge le plus favorable au traitement est compris dans la période entre 40 et 80 ans. La durée de l'affection ainsi que la dose d'insuline requise pour son contrôle permettent de prévoir les résultats; les diabètes d'origine récente, et ceux ne demandant qu'une faible dose d'insuline, offrent le meilleur pronostic.

Les accidents du traitement comprennent un certain malaise et une lourdeur gastrique, une éruption cutanée à forme vésiculaire et, à dose trop élevée, des réactions hypoglycémiques évoquant en tous points celles produites par une dose excessive d'insuline. A ce propos, les auteurs rappellent qu'en vertu de sa faculté de bloquer l'insulinase, ce médicament peut augmenter l'effet d'une dose d'insuline administrée antérieurement. On nous met également en garde contre les effets du diabète incontrôlé chez les malades ne réagissant point au tolbutamide.

Certaines recommandations sont offertes en guise de conclusion. On ne doit pas employer le tolbutamide chez les malades âgés de moins de 20 ans. On ne doit pas l'employer non plus dans les cas d'infection, ou dans les cas où le régime seul peut suffire à contrôler le diabète. On doit se méfier des maigres dont l'appétit et l'alimentation sont pauvres car ces malades sont très sensibles au tolbutamide, et peuvent verser dans l'hypoglycémie. On peut commencer le traitement à raison d'un gramme par jour, et il n'est pas sage de dépasser deux grammes par jour comme dose de soutien. Il faut être aux aguets afin de dépister l'acéto-acidose au cours du traitement même chez ceux dont la demande d'insuline est basse.

ASEPTIC MENINGITIS CAUSED BY ORPHAN VIRUSES AND OTHER AGENTS

Certain general criteria are employed in virus laboratories for interpreting the relationship of viruses to human disease. The recovery of a virus during the acute phase of illness and the demonstration of a significant increase in specific antibody during convalescence are accepted as unequivocal proof of recent infection. These findings can date the onset of infection as being in close proximity to the onset of symptoms referable to the central nervous system. Myer and his colleagues (*Ann. New York Acad. Sc.*, 67: 332, 1957) feel that such data, coupled with appropriate tests excluding other agents known to cause aseptic meningitis, constitute presumptive proof that a virus *infection* was indeed the cause of a patient's central nervous system disease. However, even here, in the individual case one cannot exclude the possibility that the clinical disease should be ascribed to another undetected agent.

Final proof that a virus causes human disease is the result of the accumulation of a number of cases which a thorough investigation establishes as being associated with infection with the new virus alone. As this occurs it becomes progressively more likely that this agent bears a true etiologic relationship to the clinical syndrome.

Along these lines, the study of specimens from cases of presumed viral infection of the central nervous system occurring during the past three years resulted in the recovery of 13 orphan and four Coxsackie viruses, all obtained from alimentary-tract material of patients with nonparalytic disease. The evidence that these agents caused aseptic meningitis indicates that at least one type of orphan virus is the cause of human disease clinically indistinguishable from nonparalytic poliomyelitis.

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VIRUS MENINGITIS—SEVEN CASES IN ONE FAMILY

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OVER THE PAST THREE YEARS several outbreaks of aseptic meningitis have been reported from America, Canada, England and N.W. Europe. At Holland, N.Y., 24 cases were reported in July 1956 by Karzon *et al.* (1956).[1] In East Suffolk, England, between September and December 1955, 11 cases were investigated by Boissard *et al.* (1957)[2] and Garnett, Burlingham and van Zwanenberg (1957).[3] Subsequently at Leicester, in July 1956, over 100 cases were admitted to the local isolation hospital by Rotem (1957).[4] The descriptive terms "Trent Valley fever" and "Nottingham meningitis" have also been applied to designate epidemics of the same malady observed locally (*Lancet* 1956).[5]

According to Hennessen (1956),[6] epidemics were reported between July and October of 1956 from many parts of North Western Europe, affecting Sauerland (Westphalia), Ruhr and Aachen. Later it spread to Holland, Belgium, Luxembourg and Central and Southern Germany. Following an accidental laboratory infection acquired through splashing virus on the lips of a worker, Hennessen observed from personal experience that the incubation period of the disease was five days. The condition was found to be commonest among German children between three and seven years of age and tended to affect districts where housing conditions were poor.

Although the existence of aseptic meningitis has long been familiar to the medical profession in Canada, there are few references to aseptic meningitis in Canadian medical literature. Isolated accounts indicate that physicians have tended to regard the disease as a non-paralytic manifestation of poliomyelitis infection.

More recently, the work of Rhodes and his associates at the Hospital for Sick Children, Toronto, has focused attention on claims for the recognition of aseptic meningitis as a clinical and virus entity distinct from poliomyelitis.[7] The latter investigated 33 cases of aseptic meningitis, and from these were recovered three strains of Type I poliomyelitis virus, 13 strains of Coxsackie B4, Dalldorf type virus, and eight unidentified viruses. Five patients suffering from non-paralytic illness were found to excrete both poliomyelitis and Coxsackie B4 viruses in their stools. The evidence in favour of the pathogenic role of Coxsackie B4 virus in the causation of aseptic meningitis was further strengthened by the recovery of three strains from cerebrospinal fluid and the fact that seven patients excreting Coxsackie B4 virus showed a rise in titre to the homologous virus in six instances.

Four of the eight unidentified agents satisfied the criteria for inclusion in the Echo group of viruses. Since they were recovered from both cerebrospinal fluid (CSF) and stools and the patients developed a rise in antibody to the homologous virus, it was assumed that these agents were etiologically responsible for their associated clinical conditions. The cases originally diagnosed clinically in 1952 as non-paralytic poliomyelitis were re-studied by Duncan *et al.* (1954),[8] (1955)[9] and subsequently re-designated aseptic meningitis by Beale *et al.* (1956).[7] On reinvestigation it was found that the material yielded three different viruses, namely poliomyelitis, Coxsackie B4 and Echo. It would therefore seem that the syndrome of aseptic meningitis could be caused equally well by either Coxsackie B4 virus or a member of the Echo group. To complicate the situation further, mixed infections by these agents are now recognized to occur, and so the problem of clinical differential diagnosis not only becomes difficult but well-nigh impossible when the facts have to be reconsidered in retrospect.

In the clinical cases which we describe below, viruses were isolated while the patients were still ill, and it was therefore possible to study a viral aseptic meningitis uncomplicated by Coxsackie B4 or poliomyelitis viruses.

FAMILY HISTORY OF OUTBREAK

The affected home was located in a relatively isolated community, 30 miles from the city of Halifax. The family consisted of eight members: the mother, aged 46; three sons: Donald S., aged 11; Clarence S., aged 14; and John S., aged 22; a married daughter, Marjorie T., aged 18; her husband John T., aged 23, and their two infants, Marguerite T., aged 21 months; and Linda T., aged 3 months.

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The mother and her three sons lived in a small frame house 20 x 30 feet, and the married daughter with her husband and two offspring were housed in an adjacent wooden structure of smaller dimensions. The domestic water supply was derived from a nearby stream and the only toilet facilities consisted of an outside privy. The coliform count of this water was 5 organisms per ml.

At this season the weather was cold and wet, with snow, ice and occasional warm intervals. Domestic animals consisted of a cat, a dog and three mink which were cared for by Marjorie's husband. Mrs. S. volunteered the statement that, since the cat was prone to sleep on the bed shared by Donald and Clarence, she associated the illness of the two boys with the cat, and acting upon her own initiative had the animal destroyed. Inquiries made through the local Medical Officer of Health, Dr. G. M. Smith, revealed that the health of the adult and child population of the area had been good and that school attendance was normal. As far as we were able to determine, there were no similar cases of illness among fellow classmates of Donald and Clarence at the local school.

Clinical Features

Case 1.—Donald S., an 11-year-old white boy, took ill on February 28, 1957. He experienced headache accompanied by pain in the middle of his back and retired to bed. The following day he felt well enough to attend school but was compelled to return home with a severe headache. He had no other complaints. Headache continued throughout the following day and he remained indoors from March 2 to 5. During this period the patient suffered persistent headache, photophobia, and retro-ocular pain together with pains in the back and some stiffness of the neck. He felt nauseated but restrained himself from vomiting since it markedly aggravated his headache. Constipation was present. On March 5 he was admitted to the poliomyelitis clinic of the Victoria General Hospital. On admission, physical findings included moderate spasm of the muscles of the back, buttocks and hamstrings, but a careful general physical and neurological examination failed to reveal any other demonstrable abnormalities.

Laboratory data were as follows: Urinalysis—negative; Kahn test—negative; Hb 14.5 g. %, leukocyte count 14,550 per c.mm. with 65% neutrophils, 33% lymphocytes, 1% monocytes and 1% immature forms. Cerebrospinal fluid examination on March 5 showed 670 cells, of which 30% were monocytes; protein was 23 mg. %. The sugar and chloride levels were normal. Bacteriological examination was negative. On March 9, the cerebrospinal fluid was re-examined and the following data obtained: 665 cells per c.mm., of which 100% were monocytes; protein was 42 mg. %. Sugar and chloride levels were normal and attempted bacteriological culture was sterile. X-ray examination of the chest was negative.

Case 2.— Clarence S., aged 14, brother of Donald S., suddenly took ill at school on March 8, 1957. He was forced to return home and retire to bed owing to severe headache located in the frontal and occipital regions. The following day he attempted to arise but experienced dizziness and his legs felt weak and heavy. He remained in bed until he was transferred to hospital on March 12. During this period he complained of pains in the abdomen and stiff neck. Severe headache persisted and he was unable to sit up because of pain and stiffness in his lower back. His arms and buttocks were unaffected but his shoulders were tender to pressure. Pain and soreness were present in the backs and sides of the legs, and the patient felt hot and feverish. Slight photophobia and sore throat were present. Appetite was good but he was prevented from sleeping by the intensity of pain affecting the head and eyes. He emphasized that his neck and the back and sides of his legs were very painful. Likewise the lower part of his back was painful when he attempted to sit up. On March 12, he was admitted to the poliomyelitis clinic of the Victoria General Hospital, Halifax. The following physical signs were elicited. The throat was slightly injected; the neck and back were very stiff. Abdominal muscles were painful and tender and showed guarding. There was marked spasm of the hamstrings and the shoulder girdle muscles were extremely tender. The cranial nerves were unaffected. Deep and superficial reflexes were normal. There was no loss of muscle function. Lymphadenopathy was present in axillæ, groins and the anterior triangles of the neck. Forty-eight hours after admission to hospital the condition improved greatly. The last symptoms to depart were the pain and stiffness of the lower back and the backs and sides of the thighs.

Laboratory data: urinalysis and Kahn test were negative. Hb value 15 g. %.; the leukocyte count was 8050 with 48% neutrophils and 44% lymphocytes. Cerebrospinal fluid examination revealed the following on March 13: 62 cells per c.mm., of which 95% were monocytes; protein 50 mg. %; sugar and chloride levels were normal. On March 16, the fluid was cloudy and contained 800 cells per c.mm. consisting of 95% monocytes. The protein was 73 mg. %; sugar and chloride levels were normal. On March 20, there were 77 cells per c.mm. of which 95% were monocytes; protein 65 mg. %; sugar and chloride levels were normal. All three specimens were bacteriologically sterile.

Case 3.—Mrs. Marjorie T., 18-year-old sister of Donald S. and Clarence S., was seized during the morning of March 12 with severe headache involving the entire top of the head. She had

sore and painful eyes with photophobia. She was forced to retire to bed because movement greatly aggravated the headache. Her shoulders, upper arms and back ached. She had transient episodes of pain in the chest and legs. In order to be comfortable she was compelled to lie quietly in bed. Vomiting or urinary disturbances were not present. Her appetite varied from day to day and she was severely constipated. She stated that she felt hot and feverish and that her eyes felt dry and sticky. The only discomfort other than her severe headache was a slight pain in the back of her neck. She had occasional episodes of delirium at night. Her condition remained unchanged until March 20, when improvement commenced. Within 48 hours recovery was complete. Cerebrospinal fluid on March 13 contained 33 cells per c.mm., of which 100% were monocytes; protein 37 mg. %.

CASE 4.—John S., aged 22, a well-developed male, woke up on March 13, 1957, with slight headache, which he described as pounding in character, accompanied by "sickness to the stomach". He stated that he felt feverish, his neck muscles were tired and his head felt heavy. He volunteered the information that, although he repeatedly pinched his muscles, he could elicit no tenderness at any site. After three days he felt better and recovered completely. No diarrhœa or vomiting was experienced.

CASE 5.—Marguerite T., aged 21 months, daughter of Marjorie T., had a past history of surgery for imperforate anus at age 5 days, and measles in November 1956. Her present illness commenced on March 14, two days after her uncle (Clarence S.) was hospitalized. Her parents had noted that she was irritable and slept poorly for the previous two weeks. On the morning of March 14, she did not awaken as early as usual but on doing so was listless, feverish (107° F.) and completely covered with a bright scarlatiniform rash. She ate poorly that day and preferred to lie quietly in her crib. The mother was convinced that the child was not experiencing pain. Late that day, she was taken to the family physician, who diagnosed scarlet fever and administered penicillin for two successive days. The child recovered completely within 48 hours of onset but the skin remained slightly rough and dry. There was no peeling.

CASE 6.—Linda T., 3-months-old sister of Marguerite T., took ill on March 15. When seen by the family doctor the child showed signs of a mild upper respiratory infection. No meningeal signs were evident. The face and upper part of the body were covered by a mild scarlatiniform rash which lasted two to three days. Fever up to 104° F. was present. A tentative diagnosis of scarlet fever was made at the time and penicillin was administered. At no time did the infant appear to be in pain.

CASE 7.—John T., aged 24, husband of Marjorie T., stated that he experienced headache starting on March 16 and lasting for 24 hours. This was severe enough for him to consult a physician, who prescribed aspirin. Notwithstanding the relatively mild illness which the patient suffered, virus was isolated from his stools on March 18.

VIRUS ISOLATION

With monkey kidney cell tissue cultures, virus was isolated from the stools of Donald S. in 48 hours, from the CSF of Clarence S. in 48 hours and from the stools of Linda T. in 72 hours. In the case of John T., virus was obtained after three passages over a period of 13 days. All four strains were readily propagated and on subsequent serial transfers the cytopathogenic effect (CPE) was invariably evident in 6 to 12 hours. Efforts to infect HeLa cells and human amnion cultures were unsuccessful. Tissue cultures were maintained in synthetic media alone and no animal sera were incorporated.

TABLE I.

Name	*Date of onset of illness*	*Date of collection of specimen*	*Specimen*	*Result*
Donald S.....	Feb. 28 1957	Mar. 8 1957	Stool	CPE
Clarence S.....	Mar. 8 1957	Mar. 13 1957	CSF	CPE
Mrs. Marjorie T...	Mar. 12 1957	Mar. 19 1957	Stool	Nil
John S.....	Mar. 13 1957	Mar. 17 1957	Stool	Nil
Marguerite T...	Mar. 14 1957	Mar. 18 1957	Stool	Nil
Linda T.....	Mar. 15 1957	Mar. 18 1957	Stool	CPE
John T.....	Mar. 16 1957	Mar. 18 1957	Stool	CPE

VIRUS NEUTRALIZATION

Virus obtained from Linda T. was tested for evidence of neutralizing antibodies against sera procured from other members of the household. The following serum dilution values were recorded: Donald S. 1/16; Clarence S. 1/128; Marjorie S. 1/128; John T. 1/64; and John S. greater than 1/256. It would thus seem that the Linda T. virus could be the same agent as that affecting others in the family.

A second series of tests was performed to ascertain whether the agents isolated from the stools of Donald S. and the CSF of Clarence S. could be neutralized by antisera to the viruses of poliomyelitis and to Coxsackie virus. No antibodies could, however, be demonstrated with antisera prepared against poliomyelitis viruses Types I, II, III, and also poliomyelitis trivalent antisera. Likewise no neutralization could be demonstrated with Coxsackie virus antisera types A9, B1, B2, B3, B4 and B5.

Acute and convalescent sera obtained from Clarence S. were tested against 100 $TCID_{50}$ of

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the homologous virus recovered from the CSF of Clarence S. and the virus isolated from the stools of Donald S. The results showed a 32-fold rise in serum antibodies from 1/2 to 1/64 in Clarence S. to his homologous virus. Likewise an eight-fold rise from 1/8 to 1/64 was noted against the heterologous virus derived from Donald S. It was not possible to obtain acute and convalescent phase sera at satisfactory time intervals from the other patients to enable comparative serological tests to be done.

Through the courtesy of Dr. D. T. Karzon, Director of the Virology Laboratory, University of Buffalo, N.Y., we received a quantity of rabbit antiserum prepared against Echo 6 prototype D'Amori virus. The tests showed that 1/10 dilution of this antiserum neutralized 100 $TCID_{50}$ of Donald S. virus. A second test, performed with Linda T. virus, also showed neutralization to Echo 6 antiserum in low titre. A strain of this virus was forwarded to Dr. Karzon, who obtained similar low titre neutralization against Echo 6 antiserum. Subsequently, we forwarded a strain of Donald S. virus to Dr. J. L. Melnick of the Echo Virus Typing Committee at Yale University, for expert opinion. Dr. Melnick duly identified this agent as Echo 9 virus on the basis of plaque morphology, *cercopithecus patas* susceptibility and neutralization properties.

In view of the findings of Boissard *et al.* (1957),[2] we tested three strains of virus isolated from our Cases 1, 2 and 6 respectively for pathogenicity to 24-hour-old mice. The results showed that in all cases a high proportion of the mice inoculated either intracerebrally or intraperitoneally developed paralysis in five to seven days. Furthermore in Case 1, the virus was serially passaged from the first to a second litter of mice and produced paralysis in 10 out of 11 mice inoculated intracerebrally and 5 out of 6 inoculated intraperitoneally. This aspect of the problem is under further investigation and will form the text of a separate publication.

DISCUSSION

There is a close similarity in some respects, and apparent identity in others, between clinical features observed by us and those reported by American, British and German authors. Severe headache, either frontal, retrobulbar or generalized, is a characteristic feature of the disease. Likewise fever was observed in all our patients.

Rotem (1957)[4] and Odenthal and Wunder (1956)[10] have stressed the difficulty in establishing a differential diagnosis from non-paralytic poliomyelitis at the onset of the epidemic. Other salient features were the presence of nuchal and spinal spasm of short duration with rapid recovery, stiffness of muscles of the neck and back with resistance to flexion, and moderate spasm of the hamstring group. There was retention of normal motor power, temporary loss of superficial reflexes and transient depression of deep reflexes. Lack of residual paresis, ataxia and headache was noted in children. Additional common features encountered were photophobia, vomiting, cervical adenitis, constipation and morbilliform rash. Recovery is complete and no death has been recorded.

The Committee on Entero-Cytopathogenic Human Orphan Viruses (1955)[11] have defined these agents as possessing the following characteristics: (1) They are cytopathogenic for human and monkey cells in culture, with preference for the latter. (2) They are not neutralized by pooled anti-poliomyelitis or anti-Coxsackie sera. (3) They are non-pathogenic for infant mice. (4) They are not related to the viruses of herpes, influenza, mumps, measles, varicella, acute respiratory disease or the adenoidal-pharyngeal-conjunctival group. (5) The Echo viruses are neutralized by human gamma globulin and human sera. (6) A number contain complement fixing antigen. (7) They vary in size from 11 to 90 mμ. (8) They display distinctive plaque formation by exhibiting diffuse and irregular boundaries.

The agents we have isolated at Enfield, N.S., have been recovered from a sharply marked clinical entity while the patients were still ill and under medical care. The disease we have encountered bore the closest resemblance to the condition described earlier by Karzon *et al.* (1956),[1] Boissard *et al.* (1957),[2] Rotem (1957),[4] Johnsson (1955)[12] and by Odenthal and Wunder (1956).[10] The designation "orphan virus" would therefore appear to be inappropriate so far as those under discussion are concerned (see Kibrick, Melendes, and Enders, 1957).[13]

The isolation of these agents from pathological cerebrospinal fluid is presumptive evidence of their pathogenicity to man. The high CSF cell counts and preponderance of monocytic leuko-

cytes reinforces the view that these viruses are the cause of meningeal inflammation, irritation and associated neuromuscular disorders.

From the taxonomic point of view, the agents now recovered could perhaps be grouped as a family with other entero-cytopathogenic viruses. It is questionable, however, whether it is justifiable to continue to designate them as human orphan viruses any more so than the virus of human poliomyelitis.

It is of added interest to mention that Boissard *et al.* (1957)[2] have revealed that the viruses isolated from cases of aseptic meningitis and thought to be related to the Echo (Hill) strain 9 virus were pathogenic to infant mice. Thus material at the first and second passage level induced paralysis in animals inoculated by the intraperitoneal route. This aspect of the problem is now under further investigation.

The recovery of viruses from cerebrospinal fluid also calls for some comment. Prior to the introduction of tissue-cultivation techniques it was notoriously difficult, if not even impossible, to isolate viruses from CSF by means of animal inoculation. Even when a suspected agent was recovered from blood, special precautions were necessary to ensure that the laboratory stocks of mice employed were not carriers of latent virus, as for example, in the case of lymphocytic choriomeningitis virus (see van Rooyen and Rhodes, 1948[14]).

Today the situation has greatly changed and tissue cultivation techniques have enabled the recovery of specific viruses from the CSF in a range of clinical affections involving the brain and meninges and exhibiting bizarre and obscure clinical symptomatology (see editorial, 1957,[15] and Crawford, 1956[16]). Indeed the stage has been reached when every suspected non-bacterial infective process thought to involve the brain or meninges should be subjected to tissue cultivation methods.

Since the virus we have isolated is paralyzant to mice and is neutralized in high titre by Echo 9 antiserum, and a rash was observed in the two cases we have studied, it is probable that the outbreak was due to Echo 9 virus, described by Boissard *et al.* (1957).[2] The recent work of Ramos-Alvarez (1957),[17] Meyer *et al.* (1957)[18] and Melnick (1957)[19] suggests that extensive investigations will be necessary before it is possible to determine the antigenic relationships of the agents we have isolated to other Echo viruses on the one hand, and to Coxsackie viruses on the other.

SUMMARY

The clinical syndrome of virus meningitis (aseptic meningitis) associated with rash in two cases is described in an outbreak affecting seven members of one family.

Four strains of an agent cytopathogenic for monkey kidney cells, but not HeLa or human amnion cells, were isolated from the stools of three patients and the CSF of one.

The virus causes paralysis in infant mice inoculated by the intracerebral or intraperitoneal route.

Sera obtained late in the disease from patients showed neutralization of the virus. In one case tests on two phase sera showed a 32-fold rise in antibody titre to the homologous strain of virus and an eight-fold rise against a heterologous virus.

The viruses isolated have been placed in the Echo 9 virus category.

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REFERENCES

1. KARZON, D. T. *et al.*: *J. A. M. A.*, 162: 1298, 1956.
2. BOISSARD, G. P. B. *et al.*: *Lancet*, 1: 500, 1957.
3. GARNETT, D. G., BURLINGHAM, A. AND VAN ZWANENBERG, D.: *Ibid.*, 1: 500, 1957.
4. ROTEM, C. E.: *Ibid.*, 1: 502, 1957.
5. Public Health: *Lancet*, 2: 838, 1956.
6. HENNESSEN, W.: *Deutsche med. Wchnschr.*, 81: 2088, 1956.
7. BEALE, A. J. *et al.*: *Canad. J. Pub. Health*, 47: 179, 1956.
8. DUNCAN, D., PEACH, A. M. AND RHODES, A. J.: *Ibid.*, 45: 396, 1954.
9. DUNCAN, D. *et al.*: *Ibid.*, 46: 1, 1955.
10. ODENTHAL, H. AND WUNDER, M.: *Deutsche med. Wchnschr.*, 81: 2090, 1956.
11. National Foundation for Infantile Paralysis Committee on the Echo Viruses: *Science*, 122: 1187, 1955.
12. JOHNSSON, T.: *Arch. ges. Virusforsch.*, 6: 233, 1955.
13. KIBRICK, S., MELENDES, L. AND ENDERS, J. F.: *Ann. New York Acad. Sc.*, 67: 311, 1957.
14. VAN ROOYEN, C. E. AND RHODES, A. J.: Virus diseases of man, 2nd ed., Thomas Nelson & Sons, New York, 1948, p. 1052.
15. Editorial: *Brit. M. J.*, 1: 811, 1957.
16. CRAWFORD, M., MACRAE, A. D. AND O'REILLY, J. N.: *Arch. Dis. Childhood*, 31: 182, 1956.
17. RAMOS-ALVAREZ, M.: *Ann. New York Acad. Sc.*, 67:
18. MEYER, H. M. *et al.*: *Ibid.*, 67: 332, 1957.
19. MELNICK, J. L.: *Ibid.*, 67: 363, 1957.

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RÉSUMÉ

On rapporte de plus en plus fréquemment depuis quelques années de nombreuses petites épidémies de méningite soit-disant aseptique connue sous des noms divers tels la fièvre de la vallée de Trent, la méningite de Nottingham, etc. Ces affections sont causées par un des virus de la poliomyélite, du Coxsackie B4, ou des virus Echo, seul ou en combinaison l'un avec l'autre. Elles atteignent surtout les enfants âgés de trois à sept ans et ont une incubation d'environ cinq jours. Les auteurs décrivent ici les circonstances dans lesquelles une famille de sept membres fut atteinte par une telle infection. Les faits cliniques sont donnés en détail dans chaque cas. Grâce à la culture des tissus basée sur l'emploi de reins de singe, le virus en cause fut isolé des selles et du liquide céphalo-rachidien de ces malades. En dépit des signes méningés assez prononcés mais transitoires, on ne put observer aucun reliquat chez les enfants. Les travaux entrepris dans le but d'identifier le virus ont montré qu'il appartient au groupe entérocytopathogène paralysant les souris chez qui on l'injecte et se rattachant probablement à la variété Echo 9.

OBSERVATIONS ON SLEEP DISTURBANCES IN PRE-SCHOOL CHILDREN*

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SLEEP DISTURBANCE in the early years of life is a common problem although the exact incidence is uncertain. Roberts and Schoellkopf (1951)[1] reported that severe bedtime or sleep problems were presented by a fifth of 783 30-months-old normal children in their Rochester, Minnesota, study. Presumably therefore, such troubles are difficult to prevent, and frequently slow to respond to treatment. It is rare for the disturbance to be so grave that it interferes over a long period with the growth and development of children. However, it can be extremely wearing on parents, so that mothers (and occasionally fathers) may reach a state of exhaustion or worse, in their vain attempts to deal with the situation. This happened to the mother of one of the children to be discussed and the devastation produced in that home by the child's disturbance prompted this presentation.

REVIEW OF LITERATURE

If such distressing experiences are so common, one would expect to find frequent reference to the problem and its management in pædiatric journals and textbooks. It was surprising therefore that in the Index Medicus, and the Armed Forces Medical Library current list, for the period 1950 to 1954 inclusive, I could find only 12 references to the subject, half of them in journals available in the library of our medical faculty, the others written in Russian or Polish, or otherwise not available. A similar experience was described by Illingworth (1951):[2] "A search . . . of the last fifty volumes of the Index Medicus, covering the world's literature for the past 25 years, revealed a mere 18 papers. Four of these were British and one was American. In contrast the last twenty volumes of the Index listed 53 papers on lipochondrodystrophy."

Spock, writing on chronic resistance to sleep in infancy,[3] drew attention to the unfortunate effects of the popular swing to "self demand" as a guidepost in the raising of children. Attention to the self-expressed wishes of the child appears to have helped to prevent many feeding problems. The same principle applied to sleeping problems may make the situation worse rather than better. The child learns by experience to take what he needs in the way of food. However, it is much more difficult, and in the early years probably impossible, for him to teach himself to give up, without "help" from his parents, all that is involved in being awake. This is understandable when one considers how a child in the second and third years discovers, each day, so much to do that is new and exciting.[4]

Anderson in "The Management of Infantile Insomnia"[5] points out the degree to which sleep disturbance in the period from 15 to 30 months seems to be related to "separation anxiety". This is the time when, according to Gesell,[6] such behaviour is to be expected, presumably as a part of normal growth. One is inclined to agree with Anderson that the disturbance has a cause—the child "realizing his dependency . . . fears being deserted and unprotected if he sleeps".

Psychoanalytic theory relating to this subject is presented in an extremely interesting fashion

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by recent writers in this field.[7, 8] Some of the factors emphasized by them will be suggested in the discussion of one or two illustrative cases.

SLEEP REQUIREMENTS

Before deciding what is a problem, one should be aware of the specific sleep requirements of the infant and child. It is quite possible that many parents expect too much help from Morpheus in freeing them from the care of their children. This matter is reviewed as it applies in the first six months, in the study "Sleep Characteristics of Infants".[9] The authors (Kleitman and Engelmann) complained about references to the sleep requirements of infants in the eighth edition of the popular publication "Infant Care" of the United States Department of Health, Education and Welfare. Here it was stated that during the first week of life the infant is awake only two hours, and that even by six months the total duration of his sleeping is 15 to 17 hours a day. Discussing their own findings these authors state:

"Although the findings of Gesell and Amatruda[10] that a neonate slept only 15 hours out of 24, seriously challenged the older notion concerning almost continuous sleep of young infants, the figures applied to only one individual, who might have been an exceptional case. Furthermore they were obtained by uninterrupted direct observation for 14 days, and this is not only costly, but is inapplicable to behaviour studies under family home conditions. On the other hand, dependence on parents' reports alone is unsatisfactory, and a combination of the latter with actograms is only a little better, if the motility records are not properly evaluated. In our study, concurrent direct observation and automatic recording of the infant's motility enabled us to distinguish between wakefulness and sleep, and thus to determine accurately when and for how long the infants were awake when presumed to be asleep . . . Our figures, gathered on 19 infants, not only confirm those of Gesell and Amatruda, but extend them to the end of the first half year of life. While our subjects as a group had a mode of 14 to 15 hours of sleep, individual infants had their own ranges of total duration of sleep, with modes as low as 12 to 13 hours and as high as 16 to 17 hours. That there was a decrease of only one hour in the total sleep in the first six months of life was also in conflict with the accepted notions of a drop from 22 to about 16 hours in that length of time."

Perhaps because of this criticism, the tenth (1955) edition of "Infant Care" is much more liberal in its description of the sleep characteristics of infants.[11]

As for children in the toddler age group, for almost 800 two and one-half year olds in the Rochester study[1] the average daily sleep was about 13 hours with a range of from 8 to 17 hours. Such wide normal variation in the sleep requirements of healthy children should be kept in mind when advising parents who complain about how little their children sleep and worry about how damaging this may be to them.

POSSIBLE ORGANIC FACTORS

Young children's sleep disturbances are obviously not all due to emotional problems or faulty parental handling. Especially if the situation is acute it is important to examine the "problem-child" for signs of distressing physical disease which may be primarily responsible. Physical disturbance commonly blamed (rightly or wrongly) includes pinworm infestation, meatal ulcer (with urethral obstruction and bladder distension), anal fissuring (with perhaps secondary constipation and fear of bowel movement), eczema, breathing difficulty from any cause, and many other painful conditions associated with inflammation or trauma. However, when these conditions are not found, or if the sleep problem persists when they have been corrected, or even in their presence, one should think of other non-organic factors as well. These vary in importance according to the age of the child.

THE RESTLESS NEWBORN

The earliest common sleep disturbance occurs in the first weeks of the association of the new parents and new baby. The strange noises produced by the normal newborn can be quite frightening to his parents if he sleeps close to them. It is likely that few parents, especially with their first child, have been able to avoid a good deal of anxiety as they listen to the snorting, gurgling and irregular breathing of the delicate being beside them. By frequently picking him up or otherwise disturbing him they may create a problem where none existed. Hence we recommend early removal of the child from his parents' room. This can be arranged even if the infant is being breast-fed, when it may be wiser for the mother to be wakened enough (as she would by going into another room to pick up the child) for her not to go to sleep with the infant beside her while nursing him.

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THE FEARFUL NINE-MONTHER

Even if the child is not removed in the early weeks, this should be done before the age of six months, since after this time the infant is much more aware of such a change in his environment and more apt to be upset by it. Sleep disturbance in the second half of the first year may well be related to the child's newly developed ability to discriminate between people, and to recognize familiar objects. This development seems to be the background for what parents refer to as "making strange", sometimes called "eight-month anxiety", although it may occur before or after the eighth month, or not at all. This type of disturbance if improperly handled may go on for months, as in our first case, in which, after 14 months of fruitless attempts to cope with the problem, the exhausted mother was in hospital with pneumonia.

This problem, so common in the second half of the first year, usually decreases with growth. It is helpful to parents to be forewarned, with also some explanation of its meaning, and advice on how to deal with it when it appears. We regularly caution them to put the child to bed, in his own crib, in his own room and at as regular an hour as possible. A night light seems to make the room less strange and frightening if he awakens, and when this happens it is wise to avoid picking him up. The mother's quietly reassuring presence in the room is often sufficient comfort, and it does not involve the activity of lifting, holding and putting down which may fully awaken an infant otherwise half asleep. Many have found rocking in a cradle (if one can be found or made!) much more effective than rocking in the mother's arms. The anxiety with strangers seems to be less marked in infants who regularly see several familiar adults, one or other of whom attend him periodically in the mother's absence, and are always seen by him on such occasions before he goes to sleep. It has been suggested that peek-a-boo games, whether initiated by infant or parent, are therapeutic, teaching him that what goes can return, and that mother still exists even when not in view. Especially important is the advice to avoid taking the child, whether infant or toddler, into the parents' bed. This is the easiest and most immediately effective thing for the sleepy adult to do—but it inevitably prolongs the difficulty since it "rewards" it.

THE SLEEP-RESISTANT TODDLER

There is frequently a return of sleeping problems between 15 and 20 months, with increasing rebellion at bedtime and also frequent night-waking. The rebellion is perhaps part of the characteristic "negativism" developing at this time, but may be greater because mobility and understanding have multiplied the exciting activities of the day which he is loath to give up. The parent must recognize for the child that he is tired and ready for bed, set for him reasonably regular bedtime hours, and make this as pleasant a giving-up as possible.[4] The familiar pattern of bedtime rituals (a kiss, a drink, a teddy) is a comfort, as is a familiar face if he awakens. As with the infant, parents are wise to avoid "rewarding" him by taking him into their bed.

ILLUSTRATIVE CASES

CASE 1.—Wendy P., aged 23 months.

Problem: Increasing resistance to going to bed, wakefulness with screaming in the middle of the night, excessive attachment to the mother, poor appetite.

Wendy was the younger of two children of relatively young parents who had been living in the same place since her birth. The father was a pharmacist, formerly a very successful "detail man" for a large drug firm. About a year previously he discovered that he had mild diabetes and for this and other reasons for some months he had been considering how best to secure a more settled occupation. A few weeks before he had purchased a drugstore in a Manitoba town 150 miles from Winnipeg where the family would soon move. Before his illness the father had weighed 215 lb., and as part of the treatment of his diabetes had managed to lose over 40 lb. This change in his appearance seemed to be as disturbing to his wife as was the discovery that he had diabetes. The mother was a graduate nurse, who characterized herself as a nervous hard worker, excessively conscientious. She had had considerable disappointment over the outcome of her five pregnancies, only two of which had produced living children. The first child was born six weeks prematurely and lived only six hours. At this time an Rh incompatibility was discovered, although there was never any evidence that this had any bearing on any of her pregnancy difficulties. The first living child (born of the second pregnancy) weighed 7 lb. at birth and 45 lb. at five years. This boy has always been good-natured and easy to handle, never presenting any eating or sleeping difficulty. The third pregnancy ended in miscarriage at three months. The fourth pregnancy terminated prematurely at seven months, the baby living eight days. One year after the death of this last child, Wendy was born, the product of a full-term preg-

nancy and a normal labour, her weight at birth being 6½ lb.

She developed satisfactorily and gained well, although she seemed to require less sleep and less food than her brother had at the same age. There were no real difficulties with her until about nine months. At that time she began to get teeth, and the ability to crawl made her more active. She also began to sleep poorly, rebelled against going to bed, and demanded a great many return visits of one or other parent with drinks, teddies, blankets and kisses. Increasingly there was a tendency for her to waken in the middle of the night and scream continuously, until she was picked up by one or other parent. In recent weeks the parents had become so distressed about this that spanking was frequent though admittedly futile. She regularly cried for her bottle at the time of her afternoon nap and at bedtime, so that it had been regularly given to her until a month before hospitalization when it was accidentally lost, and although she protested about this for one or two nights she apparently adapted without much difficulty. For the preceding three or four months she had been unusually attached to a satin blanket which she carried with her wherever she went and rubbed against her lips. For the past few months she had been sleeping in her own crib in the same room as her brother.

Wendy was a pale, thin-faced, dark-eyed, sad-looking little girl whose appearance suggested delicacy and fragility. Surprisingly, her height, weight and hæmoglobin value were quite normal for her age. The only abnormalities on physical examination were scratched mosquito bites, a slight watery nasal discharge, and on chest film a faint shadow in the upper lung field (her Mantoux reaction being negative). At the time of examination her mother had been in another hospital for several days with lobar pneumonia.

Performance on the developmental examination was quite satisfactory, considering the fact that she was examined after five days in hospital without seeing her mother. Her anxiety about this separation was evident periodically when she softly murmured "Mommy" or "Daddy" or when she pointed to the clock on the picture card and said "clock–home". She became attached to a hospital flannelette blanket which she carried with her wherever she went and clutched as she went to sleep. There was little or no sleeping difficulty in hospital, although she did cry for a while when put to bed. Although "picky" at home, she was reported to eat most of the food on the "two-year diet" which was given to her.

This girl's behaviour difficulty persisted and grew worse largely because of the way she had been handled by her parents. The mother's methods were conditioned by her serious-minded, determined, conscientious nature; her anxious delight at having finally produced a daughter; and her concern over differences in behaviour and body-build shown by her son and her daughter (probably a constitutional difference). The parents' handling of the child had no doubt also been affected by their concern during the preceding year about the husband's diabetes and the changes it had produced in his appearance and his plans. His disease had been recognized about the time her behaviour first became difficult. The little girl's wan and piquant appearance also fostered the parental tendency to indulge her whims relating to sleeping and eating. On admission to hospital she was still taking very little in the way of solid food and drinking a quart of milk a day, although she very shortly took most of the solid food offered to her.

It was suggested to the parents that some degree of sleeping disturbance is quite common in children of this age and that the treatment program involves consistency and development of a routine in relation to the child's sleeping habits. They were advised that she should be put to bed in her own room at a set time every night and with the same two or three "rituals" each night. The constancy of such a formula seems to be a comfort to a child whereas frequent changes of parental handling seem to distress the child and delay recovery. "Rewarding" the behaviour in positive or negative fashion, either by taking her into bed with them or punishing her, was discouraged. We predicted some temporary return of symptoms following discharge from hospital, possibly continuing until they were settled in their new home, which might require the use of a mild sedative. However, two months later the father wrote as follows:

"Wendy has been a fine little girl since leaving hospital. She is most independent about eating and doing other things which she didn't do before. Her appetite, attitude, everything about her has improved one hundred per cent."

CASE 2.–William B., aged 18 months.

Problem: Night waking at 3:00 a.m. for one week –stands in his crib and cries for as long as four hours, irritable for the rest of the day.

Billy was the second of three children of young parents. He had a healthy older sister of three and a new baby sister four weeks old. The father, a private in the Army, had at the time of the first visit been away on a summer army scheme in Alberta for seven weeks.

Billy was born in Toronto, birth weight being 7 lb. There was nothing unusual about the pregnancy, delivery or course after birth, until the end of the first week when he was weaned from the breast because the mother had "not enough milk". He then began to cry persistently for as long as 12 hours steadily, for which he was given phenobarbital every six hours with some relief. The family moved to Brandon when he was five months old, and he did well until he was nine months when he began to refuse to go to sleep at night. He cried steadily from early evening until midnight for the next two months in spite of sedation. This disturbance apparently stopped on its own, and there was no recurrence until the week before consultation.

This was a bright, active boy of a year and a half, physically normal with some molars erupting. He had had a normal development, except for perhaps more than the usual degree of fear of strangers. His

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mother was surprised that while he was staying with friends when she was in hospital for the new baby (a month before) there had been no sleep disturbance. She had gone into the hospital in the evening, after he had gone to sleep, and he had not seen her again for over two weeks. His night-time screaming had not developed until he had been home with her again for about a week. She was obviously somewhat harassed by the care of the three children in the absence of her husband, and noted that she had "tried everything", including spanking, which did not help. The family were living in relatively crowded quarters with two other families in the same home, so that fear of disturbing her neighbours was one of the reasons for her concern.

A mild sedative was prescribed. At the same time some explanation was given to the mother as to how the sleeping difficulty could be related to what had happened at the time of her hospitalization for delivery. It is quite likely that he feared he might again be separated from his mother in the middle of the night, waking to find himself with people not too familiar to him, and finally returning to his mother to find her with a new baby taking up all the time she previously was able to give to him. No doubt her handling of the problem was affected by the presence of considerable post-partum fatigue, aggravated by the absence of her husband. The boy's ordinarily light sleep was perhaps even lighter because of the teething. An effort was made to induce Army authorities to provide more satisfactory quarters for the family so that they might not be concerned about the baby disturbing other people living in the same home, and such a move was made about six weeks later. Within a week or two it was possible to discontinue the medicine and the boy continued well, partly perhaps because the father then returned from his army scheme.

One is inclined to believe, on the basis of the history of "colic", ninth-month resistance to sleep, and the recent difficulty, together with his daytime over-activity, that this boy is constitutionally different from his older sister, and hence his handling is more difficult. Recent experience with his baby sister (now seven months) and her sleep problem tends to support this feeling.

CASE 3.—Danny G., aged 25 months.

Problem: Resistance to going to sleep and midnight waking for seven months.

The mother related that Danny was put to bed in his own crib in his own room at about 8:00 p.m. and then insisted on calling one or other parent for as many as six or ten visits during the next one or two hours. Each time his request was different, now to sing to him, now to kiss him, now to bring him a drink, or take him to the toilet. When they tired of these trips, and stopped visiting, he would call to his father in the living room, who would call back to reassure him as many as six times, until he might finally go to sleep about 9:30 p.m. There was practically no difficulty like this if a baby-sitter were looking after him, or if visitors were present with the parents.

He would remain asleep until about two in the morning, then waken (presumably to be changed), and unless he was then taken into his parents' bed immediately, he would lie awake calling for two or three hours again. If he were being looked after by a baby-sitter and he wakened, he seemed to go quickly to sleep again even though he had not seen the sitter before he went to bed. However, when the parents returned he was immediately aware of their presence, as if he had not really been asleep at all. There had been a trial of sedation several months before, and this seemed merely to increase his anxiety and aggravate the sleeping problem (a response shown by many children at this age, perhaps as a resistance to the misunderstood overpowering effect of the drug).

For some time he had been refusing to take a nap in the afternoon, but frequently climbed into his favourite rocking chair and rocked himself to sleep there.

The parents were intelligent, healthy and quite attractive young people, the father 28 and the mother 23. They had moved into their new suite when Danny was 17 months and then for the first time he had his own room. Sleeping difficulty began a month later and at the same time the mother first realized she was pregnant. She admitted that the symptoms of early pregnancy made her somewhat more irritable and impatient with him over his bedtime demands than she might otherwise have been. There were few opportunities for outside play, and the only child with whom he had companionship was a little girl about the same age but considerably larger, who lived down the hall in the same apartment house. This girl was very poorly controlled by her parents, and among other things seemed to take special delight in making threatening gestures as if to put her fingers into Danny's eyes. Regularly when she visited she swept all his toys off his shelves, and took over in a destructive way whatever he might be enjoying. She also showed considerable interest in his urination, liked to watch him, and when he needed to go would bring the little can he used.

On the rare occasions when the parents did go out, the baby-sitter came in after Danny was asleep.

There had never been any feeding difficulty. Although he was satisfactorily bowel-trained at about 17 months, two or three months after this he began retaining his stool and having bowel movements in his pants. Within the previous few weeks he had been more regular, was placed on the toilet twice a day, given a book to read and would tell his mother when he wanted down.

Danny was a small, fair boy just over two years. He spoke quite well, with a lisp. When he became anxious during the examination, he regularly sucked his right thumb. He refused to sit at the small table, but did most of the things asked of him sitting in his mother's lap. Periodically he became quite stubborn—threw things, and then refused to pick them up although he obviously wanted them, insisting that one or other parent do so instead. If he were pressed to do this for himself, he complained of a

pain in his right foot. Once he actually lay on his back on the floor and kicked his legs, which was something he had never been observed to do before, so that his parents thought it was imitation of his problem playmate. In spite of these difficulties, his performance was reasonably satisfactory and his intelligence appeared to be normal.

It is likely that Danny's going-to-sleep problem was prolonged by the fact that the parents tolerated his demanded bedtime rituals in accordance with their own feelings at the moment. This inconsistency would of itself increase the boy's insecurity. Because they periodically left him with unknown baby-sitters, without forewarning him, and also maybe because of the boy's concern about his mother's imminent departure to have another baby, he sought to reassure himself that they were still with him, by calling them back again and again. This form of anxiety as a mother's pregnancy approaches term is quite common in children this age, even when they are taken into the mother's plans for the new baby in ways suggested by all writers on the subject. One wondered too if his night waking could not be partly a reaction to dreams about unprotected assaults from his playmate down the hall, and also partly a reaction to his fear of soiling or wetting the bed, which had been a problem not so long before.

It was suggested to the parents that they should reduce the number of rituals and make them similar each night so that he could derive some comfort from this consistency. They were advised to get in familiar baby-sitters, before he went to sleep. He then might know quite well what to expect, and not fear that any night he might awaken to find them gone. A night light was to be used in his room if he showed any evidence of being fearful of the dark. It was recommended also that the parents be quite insistent that the parents of his playmate forbid her assaults on him, and that they refuse to allow her to destroy Danny's playthings. He was to be encouraged to defend himself, and also allowed to carry out his toilet activity without her as an audience, or a potential threat to his bodily integrity. When he was wakeful in the night, they should wait to be sure that he was fully awake, and then go into his room and reassure him by their presence, but discontinue picking him up. They were further advised to stop taking him into their own bed, by doing which they were actually rewarding him for behaviour quite unacceptable to them. The parents were able to follow through on many of the suggestions made and within a week there was considerable difference in the boy. The problems gradually disappeared and did not seriously recur even after the birth of a baby sister.

SUMMARY AND CONCLUSIONS

1. Sleep disturbance in the pre-school child is common but is likely always related to, and secondary to, current physical, emotional, or environmental problems.

2. The major factors involved appear to change with increasing physical and mental growth of the child.

3. If the sleep disturbance is severe, the child will often show other behaviour difficulties for which he may be brought to the doctor, to whom the sleep disturbance is not mentioned.

4. If the physician bears in mind how much such disturbance can produce distress and fatigue in parents, he is more likely to inquire about sleeping problems in young children and attempt to deal with them.

5. The principle of "self demand" cannot be successfully applied in relation to bedtime and other sleep practices in young children.

6. When presented with a sleeping problem in a young child, the physician is well advised to pay attention to such emotional and environmental factors as separation anxiety, rigidity of habit training, increasing awareness of sex differences, and domestic disharmony and fear of family break-up.

7. Although sedative drugs are helpful, they should be used only as a temporary expedient while the total situation is being explored and adjusted as far as possible.

8. Like any other behaviour of children which is unacceptable to the parent, sleep disturbance will not disappear if it is "rewarded" in positive fashion by excessive attention, or in negative fashion by punishment.

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REFERENCES

1. ROBERTS, K. E. AND SCHOELLKOPF, J. A.: *A.M.A. Am. J. Dis. Child.*, **82**: 132, 1951.
2. ILLINGWORTH, R. S.: *Brit. M. J.*, **1**: 722, 1951.
3. SPOCK, B.: *Pediatrics*, **4**: 89, 1949.
4. WOLF, K. M.: As your child grows—the first eighteen months, The Child Study Association of America, New York, 1955.
5. ANDERSON, O. W.: *J. Pediat.*, **38**: 394, 1951.
6. GESELL, A. L. *et al.*: Infant and child in the culture of today, Harper & Brothers, New York, 1943.
7. DESPERT, J. L.: *Psychoanalyt. Stud. Child.*, **3 & 4**: 141, 1949.
8. FRAIBERG, S.: *Ibid.*, **5**: 285, 1950.
9. KLEITMAN, N. AND ENGELMANN, T. G.: *J. Appl. Physiol.*, **6**: 269, 1953.
10. GESELL, A. L. AND AMATRUDA, C. S.: Embryology of behaviour—the beginnings of the human mind, Harper & Brothers, New York, 1945.
11. UNITED STATES CHILDREN'S BUREAU: Infant care, 10th ed., United States Department of Health, Education and Welfare, Washington, D.C., 1955, p. 36.

RÉSUMÉ

Les troubles du sommeil dans l'âge pré-scolaire présentent un problème fréquent mais mal documenté, que l'on tend à ignorer en général. Il est bon que les parents soient mis au courant des variations dans le nombre d'heures qu'un enfant doit consacrer au sommeil à mesure qu'il grandit. Certaines notions assez répandues, comme celle qui prétend qu'un nourrisson doit dormir vingt-deux heures sur vingt-quatre sont mal

fondées et peuvent alarmer des parents inquiets. L'insomnie peut avoir une cause physique comme l'oxyurase, un ulcère du méat urinaire, une fissure anale, une dermatite, etc. Les nourissons normaux produisent en dormant certains petits bruits de suction, ronflements, soupirs, dont il ne faut pas tenir compte et pour lesquels on doit bien se garder de les réveiller en les prenant dans ses bras. A mesure que l'enfant apprend à reconnaître son entourage, la présence d'un visage non familier peut le tenir éveillé. La régularité dans les habitudes semble le meilleur moyen d'éviter cet inconvénient. Si le manque de sommeil a une cause émotive, le petit malade présente habituellement aussi d'autres problèmes de comportement. La quantité de nourriture qu'il prendra dépend de son appétit, mais on ne peut se fier à son besoin de repos pour les périodes de sommeil car les heures de veille ont beaucoup à offrir à une intelligence qui s'épanouit. On doit donc l'aider à dormir en lui indiquant l'heure de se mettre au lit en accompagnant son coucher d'un certain rituel agréable qu'il reconnaîtra chaque soir. Il ne faut recourir aux sédatifs qu'en des circonstances expectionnelles; ils ne doivent pas former la base du traitement.

THE CLINICAL INVESTIGATION OF PACATAL IN OPEN PSYCHIATRIC SETTINGS*

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MEPAZINE or pecazine (N-methyl piperidyl-(3)-methyl phenothiazine), a substituted phenothiazine compound, is known by the commercial name of Pacatal§ in Canada, Great Britain, the United States and Germany; and by the name of Lacumin in the Scandinavian countries.

Synthesized by Schuler and Nezel, Pacatal was the best of eight synthetic compounds tested pharmacologically by Nieschulz, Popendiker and Back[15] in terms of sedation, antihistaminic, antiemetic, antispasmodic, and energy reduction action, as well as in terms of animal toxicity. Animal experiments also showed marked inhibitory action on secretion, with a slight mydriatic effect, inhibition of normal intestinal peristalsis, a local anæsthetic effect higher than that of procaine, a sedative effect that was marked on high doses and produced somnolence; a mild anticonvulsive effect when tested with compounds such as nikethamide (Coramine), pentylenetetrazol (Metrazol), and strychnine; slight depressive effect on temperature, and negligible effects on metabolism. There was considerable potentiation of analgesic and narcotic action.

In the human, it has both parasympatholytic and sympatholytic actions, with a predominance of the parasympatholytic. It therefore has a marked atropine-like action.

The first clinical investigations were of its analgesic, anæsthetic, preoperative actions, and its effects in deep sleep.[10] In 14 normal subjects, Kleinsorge[9] found a fall of basal metabolic rate (B.M.R.) and blood sugar level, without a simultaneous fall in blood pressure, pulse, or temperature rate. Horatz used it in 1144 cases as premedication and in general anæsthesia, and prefers it to morphine-atrophine.[6] The same author prefers this drug for potentiation of hibernation anæsthesia.[7] The psychiatric literature will be discussed later.

PROJECT

Pacatal was tested in the open wards of the psychoanalytically oriented psychiatric unit of Queen Mary Veterans Hospital for a 10-month period from March 1956 to January 1957; and from July 1956 to January 1957 in the day hospital and in-patient psychiatric service of the Jewish General Hospital. The high doctor-patient ratio, the ward setting, orientation and structure have been described in detail elsewhere.[17, 20, 22, 23]

Forty-two patients were studied during this period. We believe this paper to be the first concerning a study of Pacatal in open psychiatric settings.

Research design: Research design was that previously described[17, 20, 22] and used in our other drug research.[17-23] Briefly, it consists of selecting patients with marked disorders of affect, irrespective of diagnosis. The clinical pharmacological profile of the drug is then determined, and the effect of this pharmacological profile is observed on the various aspects of

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TABLE I.—DIAGNOSIS IN 42 PATIENTS

Group I (Q.M.V.H.)			*Group II. (J.G.H.)*		
Obsessive-compulsive reactions		2	*Schizophrenic reactions*		4
with somatization			paranoid type	3	
Depressive reactions		7	catatonic type	1	
depressive reaction	1		*Anxiety reactions*		3
with agitation	2		in schizoid personality	2	
in obsessive-compulsive personality	2		in passive-dependent personality	1	
in schizoid persons with phobic elements.	1		*Depressive reactions*		4
psychotic depressive reaction, fractured right wrist, carpal tunnel syndrome	1		with somatization	2	
Manic depressive reactions		3	with agitation	2	
hypomania	1				
depression	1				
mania	1				
Schizophrenic reactions		7			
schizo-affective type	2				
paranoid type	5				
Drug addiction (barbiturates, alcohol) in a case of schizophrenia with paranoid trends		1			
Paranoid reactions in chronic brain syndrome (cerebral arteriosclerosis), auricular fibrillation, and acute cerebral hypoxia.		1			
Anxiety reactions		7			
in schizoid personality	2				
in passive-dependent personality	2				
in obsessive-compulsive personality	1				
in sociopathological personality	1				
in sexual deviant (homosexual)	1				
Conversion reactions		3			
with grand mal seizures	1				
in schizoid personality	2				
Total		31			11

affect displayed by the patient, which are the "target symptoms"—a term used by F. Freyhan for a psychiatric symptom which it is hoped will be acted upon, or modified, by a drug. Knowledge of psychodynamic, milieu, and sociological factors, from the data obtained by psychoanalytically oriented psychotherapy, as well as the natural course of the illness under psychotherapy in our hands, is used to differentiate between the relative effects of the drug and those of psychotherapy or other non-specific factors.[22, 23] In short, the physiological effects of the drug and their action on the emotion displayed by the patient or energy output, and on the physiological concomitants of anxiety, are evaluated. It is important to distinguish the immediately clear-cut pharmacological action of a drug and to attempt to evaluate this in reference to the total therapeutic outcome, for a drug may or may not be of determinable effect on the therapeutic outcome, even though its pharmacological effects are present.[22, 23]

Two groups of patients were studied. Group I consisted of 31 in-patients at Queen Mary Veterans Hospital, and Group II consisted of 11 patients at the Jewish General Psychiatric Day Hospital.

Research routine:[17, 21, 22] This included multiple, independent observations by nurses and doctors. Data were collated by the director of psychiatric research who was not one of the physicians treating the patients. Screening tests for toxicity were done before drug administration, and then weekly. They included weekly red cell, white cell, differential, and platelet counts, determinations of hæmoglobin, serum proteins, serum globulin, A/G ratio, fasting blood sugar, prothrombin time, serum bilirubin, cephalin flocculation tests, and urine analysis. Blood pressure, pulse, respiration, and temperature were determined once or three times daily, depending on the route of drug administration. Patients did not receive other organic adjuvants while on this study.

Psychotherapy: Our ordinary psychotherapy routine was continued. The drug was the only variable introduced into this otherwise formalized technique. The reasons for this have been discussed at length in our other publications.[17, 20, 22] It would have been artificial to pretend to "stop psychotherapy" since much psychotherapeutic interaction would have resulted from the ward and occupational therapy program, and from the interpersonal relations on the ward. This would have introduced a second variable.

CRUDE DATA

Group I (Q.M.V. Hospital)

Of the 31 patients (one female, 30 males), one was in his 20's, 11 were in their 30's, nine in their 40's, seven in their 50's, and three in their 60's; range 25 to 62 years.

The diagnostic categories are shown in Table I. It should be remembered that patients were selected because of marked disorders of affect irrespective of diagnosis.

MAIN SYMPTOMS

The principal symptoms of the 42 patients were anxiety (16 patients), agitation with depression (8), agitation (6), depression and anxiety (6), hypomania and mania (5), catatonic excitement (1).

Weight, blood pressure, temperature, pulse, respiration, and laboratory data: Fourteen patients (11 patients in Group I, and three of the seven patients in Group II who were on Pacatal

TABLE II.—DRUG DISCONTINUED IN 6 DAYS OR LESS (13 CASES)

Group I.		*Group II.*
Body image distortion with panic	0	1 (Case 3 - 2 days) In a case of agitation with depression.†
Panic reaction* Case 1 - 5th day	1	
Paranoid reaction with distortion of the physician's motives* Case 28—after 5 days	1	
Increased depression with agitation*† Case 2 (given E.C.T.)	1	1 (Case 9) Agitated and suicidal—5 days. Given E.C.T.
Given inadequate dosage to control their symptoms† 1 committed (Case 3) 1 given E.C.T. (Case 10)	2	1 (Case 8 - 1 day, 3 doses) Catatonic excitement.† (See also Case 3 above).
Left hospital of own volition, or transferred to another hospital Cases 4 and 24.	2	1 (Case 11) Schizophrenic, paranoid with agitation. Agitation controlled 4 days i.m. Transferred to another hospital.‡
Committed because too ill for open setting‡ Case 7	1	
Discontinued because of erythematous eruption in an allergic patient Case 16 - 6th day.	1	
Total	9	4

*These reactions are transference phenomena and have been described in detail in our other publications.[17-23]

†These cases occurred early in our study (all in first 10 cases), and were not given doses of Pacatal adequate for their symptoms. If they had occurred later when more experience had been accumulated, it is felt that most, if not all, would have had their symptoms controlled by the drug.

‡All of these patients had their "target symptoms" controlled, and left either because of this or were transferred to institutions better suited to their particular needs.

Administration was oral or intramuscular. The range was 100 to 800 mg. q.i.d. The lowest dose was 100 mg. q.i.d. (one case); the highest was 800 mg. q.i.d. (one case). Average for 31 cases was 212 mg. q.i.d.

The average duration of treatment varied from three to 164 days. Nine patients were on the drug from three to six days (dealt with separately—see Table II), and one patient was on the drug for 164 days. Average for 22 patients was 39 days.

Group II (J.G.P.D. Hospital)

Of the 11 patients (10 females, one male), the average age was 37 (range 15 to 64 years). The average duration of treatment was 21 days (1-49). (The four cases on the drug for three to six days are dealt with separately—see Table II.) The average dose was 150 mg. q.i.d., given orally or intramuscularly (75-200 mg.).

for longer than six days) showed a considerable weight gain, as compared to patients not on the drug (at least 4 lb. more than the others).

There were no major observable changes in temperature, pulse, or in respiratory rates, or in blood pressure in this series. White cell count rose in some cases, in the vicinity of 7000-11,000. This was probably not attributable to the drug. There were no other signs of toxicity in our laboratory findings.

Of the 42 patients, 34 showed a "good result on affect," eight patients showed a "poor result on affect" (six "poor," two "no change"—"no change" was considered as a "poor result").

Subjectively, 33 patients felt that they were "helped" by the drug. One felt he was "made worse," eight felt "not helped" (six "not helped", two "pills no good"). Only one patient felt "not helped" while we felt the result on affect to be "good". There was agreement between physician and patient in all other cases.

The main changes produced on the target symptoms were—reduction in energy output and motor activity (27 patients), reduction in anxiety (26), improvement in sleep (27), better appetite (15). Fifteen patients felt "more relaxed and calmed". Agitation was controlled in seven patients, while four patients showed alleviation of depressive symptoms. Seven patients lost their "tremor and shakes". Two patients had their asthma attacks markedly reduced.

Many of the above changes were produced by the interaction in our setting of the drug, psychotherapy, and the protective hospital milieu. The total changes on complexes such as depression and anxiety are therefore not attributed to the drug alone.[18-20, 22, 23]

The eight cases of "poor result on affect" are analyzed in Table III.

TABLE III.—"POOR RESULT ON AFFECT" (8 PATIENTS)

Group I.
Case 1—Panicked (see Table II).
Case 2—"No change." Inadequate dosage (see Table II).
Case 3—"No change." Agitation. Inadequate dosage for agitated patient (see Table II).
Case 10—"Poor result." Drug withdrawal in a schizophrenic. Inadequate dosage (see Table II). (Given E.C.T. after six days.)
Case 28—"Poor result." Paranoid distortion of physician's motives. Developed headache, blamed doctors and nurses. Left hospital against advice—five days (see Table II).
Group II.
Case 3—"Pills don't help" ("no change"). Agitation, depression. Developed body image distortions after two days. Inadequate dosage (see Table II).
Case 8—"Poor result." Catatonic excitement. One day—only two 50 mg. doses i.m. Inadequate dosage (see Table II).
Case 9—"Poor result." Depressive reaction with paranoid trends and suicidal drives. Remained unchanged after five days. Given E.C.T. ("Too ill"—see Table II.)

Natural course of the illness: The "natural course of the illness under psychotherapy in our hands" was changed in only five cases. Four patients with mania or hypomania remitted to their pre-morbid state within 31 days (Group I: Cases 12, 14, 19; Group II: Case 10).

One patient with schizophrenia, schizo-affective type (Group I, Case 31), had her motor overactivity controlled and was able to function better for five months, although hallucinations, delusions and dissociated thinking were unaffected.

Only clear-cut and indisputable changes in the expected course of the illness, that could not be attributed to other causes, were classed here in our study. This is similar to our findings with reserpine and chlorpromazine.

Side-effects and toxicity: Side-effects included dry mouth (21 patients), dry throat (16), "sore throat" (7), blurred vision (12), constipation (8), "stomach upset" (heartburn, "burning," dyspepsia—10), vomiting (2), nausea (1).

Less numerous were stuffiness of nose (4 patients), erythematous eruption (3 patients—face, 1; hands, 1; hands, buttocks, thighs, legs, feet, 1), "burning of face" (1), "flushing of face" (1), œdema (3 patients—face, 2; fingers and hands, 1), dry skin with scaling and peeling (3), mucosa of mouth cracked (1), dry conjunctiva and conjunctivitis (2), "itchiness of eyes" (2), "dry cough" (3), atonic bladder (1).

In one patient (Case 16, Group I) with a diffused erythematous area involving buttocks, thighs, and lower limbs, and with œdema of the hands, the drug was discontinued on the sixth day on the advice of a dermatological consultant.

All other side effects, while often unpleasant, necessitated a reduced dosage only in the rare case. Most patients were able to tolerate them under psychotherapy.

RESULTS

Clinical, physiological, and pharmacological effects (for numerical break-down, see "crude data") were as follows:

1. In adequate dosage the drug tends to reduce energy output (i.e., energy available for muscular activity).

2. In adequate dosage, it slows down and sedates many patients. Many feel tired, weak, and occasionally dizzy.

3. It stops motor overactivity, if a sufficient dosage is used.

4. It leaves the sensorium clear at all doses. The patient's capacity to think and to concentrate is retained when this was originally unimpaired.

5. In the overactive patient, it tends to slow down spontaneous movements such as pacing the floor, tremor, hand wringing, and fumbling.

6. It does not seem to change affect-tinged impulses *per se*, but tends to lessen the energy available for translating the impulses into action as compared to thought (if dose is adequate).

7. Appetite seems good in most patients on this drug. A considerable weight gain is seen in a large number.

8. Though other authors report euphoria,[1] the drug did not produce euphoria in this series, nor does it seem to carry a high risk of addiction. There was some evidence of increased tolerance in a few patients as measured by a lessening of the side effects.

9. It does not have a marked hypnotic effect, but can improve the patient's ability to sleep, especially after the first few days. It makes some patients moderately drowsy, especially after i.m. administration.

10. Patients can fight sleep when it is induced. Many patients are not made drowsy, and patients with severe insomnia sometimes need a barbiturate at bedtime.

11. It does not produce marked hypotension in doses used. Patients can usually, therefore, remain ambulatory even when there is marked reduction in energy available for muscular activity.

12. No significant changes in pulse, blood pressure, or respiration were produced in this series.

13. Psychotherapy and transference played an important role in the therapeutic process.[18, 19, 22, 23] When the drug effect was clear and overriding, transference played a secondary role, e.g. in manic patients. In most patients, however, it was very important.

14. Manic or hypomanic patients complained less of the side effects than did other patients, although side effects were present.

15. No significant toxicity was found on laboratory screening tests in this series.

16. Pacatal has a marked atropine-like action (increased sympathetic tone). This effect is so constant that it is considered to be part of the pharmacological profile of the drug.

Side effects:

1. When marked, the atropine-like action was considered a side effect.

2. Though it is a constant finding, patients vary greatly in their sensitivity to the atropine-like action. Nearly all patients showed varying degrees of dry mouth, dry throat, inability to accommodate for close vision (blurring of vision), a relative decrease in intestinal peristalsis, and a relative decrease in frequency of micturition. These were considered as side effects only when marked enough to produce subjective complaints clinically observable. Side effects are listed numerically under crude data.

Drug discontinued after three to six days: Table III refers to nine patients from Queen Mary Veterans Hospital, and the four patients from the Jewish General Hospital who were on the drug from three to six days.

In the Q.M.V.H. group it is important to note that the first four cases studied in our series fall into this category. These early cases were given doses inadequate for the control of their symptoms. All of these cases (with the exception of the one patient who left for transference reasons unrelated to dosage) were among the first 10 cases studied in our series. By then, sufficient experience as to dosage level permitted better handling of the drug.

CASE ILLUSTRATIONS

An example of a "poor result on affect" due to inadequate dosage is given to illustrate this problem:

Group I—Q.M.V.H.: Case 10. Mr. C.B., a 32-year-old, white, Roman Catholic male patient had had many previous admissions to the psychiatric unit with the diagnosis of "drug addiction (barbiturates and alcohol) in a case of schizophrenia, undifferentiated, with paranoid trends. (Former morphine addict.)"

This patient had stopped taking barbiturates and alcohol several days before admission. He presented withdrawal symptoms characterized by intense anxiety, which are described below.

On this admission, he showed marked anxiety, salivation, an obvious gross tremor of the extremities, marked psychomotor retardation, marked covert hostility which he expressed in a slow passive way and with a sullen attitude by verbal threats such as "I'll go over your head—I have political friends," etc.

He attempted to be sociable with the other patients but was quite hostile to nursing and medical personnel. The first night he was intensely agitated, tossing in his sleep, and he awoke on many occasions. Many episodes of alleged "sleep-walking" occurred during which he went to the beds of other patients to waken them. He had disturbing dreams, the context of which was thinly disguised homosexuality. The second morning he showed the above-described agitation, and talked to himself continually. By the third night he showed the same behaviour, "wandering in my sleep" to the beds of other patients, and would always claim that he was "lost" when he was "awakened".

He showed dissociation of affect, with an expressionless face, although intense agitation was seen in his motor and general behaviour. By the third night he stated, "I feel terrible, I can't stand this much longer." He was extremely restless,

shouted out in terror, and needed an orderly with him continually.

On completion of admission routine, he was given 300 mg. of Pacatal per day (100 mg. t.i.d., i.m.) for six days. Despite this, he showed the above-described behaviour, and by the end of the sixth day was so agitated that the drug was discontinued, and E.C.T. substituted.

Comment: This patient was treated early in our study, and as a result received doses inadequate to control such symptoms. Higher doses should have been used to see what their effects might be. We should have begun with 600 mg. or more per day parenterally instead of the 300 mg. per day. Had this case occurred later in our series, it is probable that higher doses would have succeeded in controlling it.

We classified this case as an example of inadequate dosage due to inexperience with the drug, and one might infer that patients with drug withdrawal reactions who show intense agitation will probably need high dosage levels if Pacatal is to be used.

An example of a case of manic depressive psychosis, manic phase, in which the symptoms were well controlled by Pacatal is now summarized:

Group I—Q.M.V.H.: Case 12. Mr. C.W., aged 52, had been known to have two previous manic episodes for which in the past he had been hospitalized elsewhere. This married, white, Protestant patient had been discharged from the surgical service of Q.M.V.H. after a cholecystectomy approximately three weeks before.

He appeared at the admitting office during the night, dressed for a "fishing trip". Because of his cholecystectomy, he had lost his position as superintendent of a block of flats, and had had to vacate his own flat. He had marked marital difficulties at the time. Admitted to the psychiatric unit, Q.M.V.H., he was alert and jovial, remarking "I never felt better in my life." He displayed great motor overactivity, pacing the room, being unable to sit in a chair, writing words on scraps of paper or on the back of cigarette boxes, and then throwing the boxes and scraps of paper away. He made numerous attempts to light cigarettes, but he was never able to complete them. He showed a marked push of speech, with short sentences and marked flight of ideas. He was oriented as to time, place, and person, but his judgment and insight were markedly impaired. A sample of his speech is quoted: "Decided to go fishing with my dog, a Beagle. A wonderful dog. Had him on a lead. Must phone my sister about him. Her husband committed suicide last September. All my family is highly strung. My wife is. I must give compassionate love."

He was given 200 mg. of Pacatal q.i.d., many of the doses being i.m. for the first five days. At the end of the first 12 hours there was little change in the patient except that he seemed less hostile to his physician and more co-operative. By the end of the first 24 hours there was very noticeable motor slowing. His speech and flight of ideas were unchanged. His mouth was dry, but he retained the ability to accommodate for close vision. On the second day, although his motor activity had further slowed, his mental state had not changed. He refused oral medication and received all his medication i.m. By the third day his flight of ideas was less excessive; he was less overtly hostile to his wife; his motor activity was markedly reduced. He could now lie on his bed and sit on his chair for more than half an hour at a time. He was sleeping well and eating well. He had a markedly dry mouth and mild constipation. He got considerable relief from the dry mouth by sucking a lemon. At this point some of the Pacatal was crushed and served in ginger ale.

By the fourth day the motor activity, speech, and flight of ideas were markedly reduced. The i.m. injections were proving painful, and an area of moderate induration was noted in the left buttock. The patient ran a slight temperature and penicillin was administered. The dry mouth and moderate degree of constipation continued. By the sixth day his activity was still further reduced; he felt somewhat "tired," and although his thoughts remained incoherent, the flight of ideas was markedly diminished. Nausea appeared as a side effect, in addition to the dry mouth and constipation. By the seventh day his symptoms had further diminished, so that the oral dose was reduced to 100 mg. t.i.d. By the 10th day the reduction in energy output and motor overactivity was further evident. The patient's thought processes, which up to then had been poorly organized, became more coherent, and he began to discuss clearly and think clearly about his home relations. Much material about his relationship with his wife appeared.

By the 16th day of medication the patient's judgment and insight improved considerably; he realized that he had been mentally ill, and stated that although he had acted as though he were happy, he had in fact felt "most miserable". He felt tired, and dizzy at times, and had lost weight during the first 16 days.

After a weekend visit at home he had a mild recurrence of his symptoms. He had had several arguments with his wife.

On the 18th day he showed some blurring of vision at times, slept well, ate well, and no longer presented motor overactivity. He was cheerful during the evening, although he would become unhappy after a visit by his wife, and once commented, "I wonder if I am wanted at home." In psychotherapy he was able to face some of his aggressivity towards her. By the 27th day he was showing interest in the details of the drug, wondered about "my pills", and asked for pharmacological data. He was most co-operative in describing his symptoms and reactions to medication at this point.

Medication was discontinued after 31 days, at which point the patient was looking forward to discharge. There had been no appreciable change in blood pressure, pulse, or respiration, or in temperature, with the exception of the fever caused by the gluteal cellulitis. His weight had returned to normal by the 31st day.

Comment: This is a good example of a manic patient who received adequate dosage to control his symptoms. The importance of psychotherapy and good interpersonal relations is also illustrated here. This case is a good example of the principle of heavy dosage level for markedly disturbed patients with motor overactivity and agitation. Lower dosage would have constituted a misuse of the drug in this type of case.

It is interesting to note that the small number of manic patients in this series, as well as those reported on by Bowes,[1] tolerated the atropine-like action and side effects of Pacatal relatively well. Most neurotic patients do, however, comment on the side effects to a greater degree. This patient remained ambulatory to a much greater degree than he would have done with chlorpromazine or reserpine. This was the case with all our patients.

It is important to distinguish between the immediately clear-cut pharmacological action of a drug (and attempt to evaluate this) and the total therapeutic outcome, since a drug may or may not be of determinate effect on the therapeutic outcome.[18, 22, 23]

Despite its leaving the patient ambulatory, the drug very adequately controls motor overactivity and agitation, and is most useful for manic and hypomanic patients.

Psychotherapy and transference are always important.[17-23] An example of a patient who tolerated marked side effects because of his good relationship with his physician is now quoted to illustrate this point:

Group I—Q.M.V.H.: Case 5. Mr. J.O., a 37-year-old patient, was admitted with a level of anxiety that almost approached panic. He showed sweating, dilated pupils, and a moderate degree of agitation characterized by pacing of floor, cracking his knuckles, and a coarse tremor of his hands. He was given 200 mg. of Pacatal p.o., q.i.d.

There were no changes in blood pressure, pulse, or respiration. The level of motor activity was moderately reduced so that the pacing, hand wringing, and knuckle cracking disappeared. The patient felt more relaxed, tired, somewhat tremulous, and much more comfortable, and slept better by the third day. At this point he developed, with increasing severity for the remaining 33 days of drug administration, the following side effects: Dry mouth, increased thirst, difficulty in accommodating for close vision, dry conjunctiva, dry cornea; red, inflamed eyes, inability to read, a "burning sensation" in his abdomen, and complete absence of perspiration. After the tenth day he developed a uniformly dry skin with cracking and desquamation of the palms of the hands and feet. The eyes continued to be red and sore, the larynx became dry, and the patient's voice became hoarse on the 20th day and remained so for the remaining 13 days.

The patient became moderately despondent at the severity of these effects, but nevertheless felt that his anxiety was controlled. He greeted his physician with a grin, and ruefully enumerated the above-mentioned formidable list of side effects.

Comment: This passive-dependent patient tolerated a level of marked side effects because of his need to please his physician by doing what he felt the doctor wished him to do, i.e., take the pills. He did this fearing loss of the physician's love and wishing to avoid his anger. For this goal he tolerated a level of discomfort and suffering that most patients, without the above-mentioned transference needs, would not have tolerated.

Here again, the pharmacological action of the drug was not different from that in some cases with bitter complaints about similar side effects. But the patient's need for love and acceptance by parental figures at almost any cost, coupled with the fear of withdrawal of this love, was expressed in the current situation.

He welcomed his discomfort, as well as the energy-reducing action of Pacatal, as visible evidence of being in the "doctor's power". For as long as he could please the physician and thereby maintain the benevolent attitude by pleasing him, he felt love, support, and gratification of dependency needs to be guaranteed.

This example is quoted to show that it is not the presence of side effects or of pharmacological action that determines the therapeutic outcome. It is rather the personal meaning to the patient of the drug action, which is always incorporated into the patient's total situation, that is important.

An asthmatic patient had an interesting result:

Group II—J.G.H.: Case 5. A 48-year-old white, female, married patient, with schizophrenia, paranoid type, who had had asthmatic attacks every second or third day before admission to the Jewish General Hospital, was given Pacatal 150 mg. p.o. for 30 days. She had no asthmatic episodes during that period. On admission she had marked anxiety, delusions of persecution, insomnia, and asthmatic attacks every second or third day.

On Pacatal she became calm, slept and ate well, and was free of asthma. There was no change in blood pressure, pulse, respiration or temperature. There was no significant change in weight, and no toxicity. A dry mouth was the only side effect. No conclusions can be reached from this case, but the atropine-like action may be of some consequence in asthmatic patients.

An example of the atropine-like action in a patient in the senium follows:

Group I–Q.M.V.H.: Case 15. A 60-year-old white male patient developed urinary retention with palpable globular bladder, and 900 and 400 c.c. of urine was removed by catheterization. The patient had been able to infrequently dribble small quantities of urine. He had an extremely dry mouth, dry throat, with difficulty in swallowing, dry larynx, hoarse voice, dry skin and dry conjunctiva.

It is important to note that this patient was 60 years old, and had had a moderate degree of benign prostatic hypertrophy. Endoscopy and cystoscopy were performed before it was concluded that the drug was responsible for his urinary retention.

Comment: This case illustrates the need in *all* patients, but especially in those who are in the senium, for close, careful supervision while on Pacatal. This is especially true in terms of care of the bowels and the urinary tract, since the elderly patient tends normally to have some degree of atonic colon with tendency to constipation and impaction. It also illustrates how devastatingly severe and troublesome some of the atropine-like action of this medication could be in such patients without proper supervision.

With proper supervision, however, this drug is extremely useful and there is no reason for not using it judiciously in the elderly patient.

DISCUSSION OF THE PSYCHIATRIC LITERATURE

Kleinsorge[10] used Pacatal with barbiturates for deep sleep or, to use his term, "therapeutic sleep", in the treatment of angina pectoris, vasomotor headache, bronchial asthma, spasms, early peptic ulcer, and other conditions. Sometimes he combined it with *Rauwolfia serpentina*. He claims good success with this.

Horatz[7] has reported on more than 5000 cases of its use as premedication for general anæsthesia, and for hibernation anæsthesia.

Werenberg[25] reports on 100 long-term psychotic patients (15 years in hospital–51 females and 49 males). He states, "The drug proved of convincing therapeutic value, improvement being obtained in 85% of the patients who had previously proved almost totally refractory to any further treatment. Furthermore, this improvement was absolutely striking in 14%." One of his patients developed fatal agranulocytosis, one of his patients died of unknown causes, and two died in the surgical department of embolism of the pulmonary artery. Werenberg states that after the drug was withdrawn, nearly all his patients relapsed within one month.

Any new procedure in treating psychotic patients in a mental hospital tends to temporarily improve many of them if it is administered by an enthusiastic and sympathetic team. (See the work of Wittkower and La Tendresse[26] in the Verdun Protestant Hospital, using no drugs at all.)

Kline and Jacob reported extremely toxic results with Pacatal,[11] but later acknowledged that this was presumably due to an impure preparation.[12]

Bowes reported on 250 psychotic patients treated with Pacatal, in a Canadian veterans' mental hospital.[1] He was enthusiastic about Pacatal as a "useful, pleasant, and euphoriant drug". He reported fluctuation in the white cell counts. He had no cases of agranulocytosis, but two patients developed leukopenia. In our small series of manic and schizo-affective patients, symptoms of overactivity were well controlled, and confirmed Bowes's general statement that the manic patient responds well to adequate doses of Pacatal.

Braun[2] reports good results with four patients at the Cleveland State Hospital who were resistant to other types of therapy. His series was too small to warrant drawing conclusions.

Feldman, in a comparative study of chlorpromazine, Pacatal, Frenquel, chlorpromazine with reserpine, and reserpine,[4] found Pacatal useful in the selected patients, although he placed its usefulness below that of chlorpromazine, and combined chlorpromazine-reserpine.

Mitchell[14] stresses that jaundice, hypotonia, and neutropenia had occurred in 16 of 37 chronic female psychotic patients whose average age was 59.5 years. One 61-year-old patient died of agranulocytosis after a thumb infection. Mitchell therefore felt that Pacatal was a dangerous and toxic drug. Here again one sees the need for careful supervision of elderly patients. One may wonder about the validity of drawing conclusions on the normalcy of response to a powerful pharmacological agent in backward chronic patients in a mental hospital who, in terms of food intake, motor activity, skeletal structure, and "psychophysiology of emotion", may or may not be similar to less chronic patients.[8]

An active correspondence on Mitchell's paper followed[3, 13, 24] in which three separate groups of authors representing different mental hospitals in Great Britain reported their experiences, all

of which were favourable to Pacatal, and in which all report it to be a useful drug.

Several fatal cases of agranulocytosis have been reported in the literature. All occurred in mental hospitals, many in elderly and backward patients. Feldman[5] reports one case, Mitchell[14] reports one case, Parker[16] reports one case. Werenberg reports one case.[25]

In the 42 patients in our study, no serious irreversible atropine-like side effects were found, nor did we see any marked fluctuation in white cell count, although there was an unexplained tendency for several patients to have elevated counts varying from 7000 to 11,000. This may have been an incidental finding, corresponding to upper respiratory tract or other virus infections, but we are not certain of this. No other laboratory toxicity was found. The absence of serious toxic effects that were irreversible in this series is, we believe, at least partially due to the careful supervision of the individual patient and the weekly laboratory data collected. Otherwise, it would be easy with this, as with any other tranquillizing drug, such as chlorpromazine and reserpine, to run considerable risks with some patients. One may conclude that under proper supervision (periodic blood counts, etc.) in a physically healthy patient whose nutritional intake has been good, Pacatal is not an unduly dangerous drug.

Therapeutic outcome: As commented on in our other publications on drugs,[17-23] the pharmacological effects of a drug are not by themselves the sole determinants of a "good" or a "poor" therapeutic result. The meaning to the patient of the physiological effects of the drug, in reference to his total situation, is what determines whether a good or a poor therapeutic outcome occurs, since this physiological meaning, if threatening, in its turn can liberate charges of energy through incompletely known neurophysiological pathways. This latter can, if it occurs, often excite rather than "calm" or tranquillize the patient.[18, 19, 22, 23]

Indications:

1. It is indicated for symptomatic relief of psychomotor excitation and overactivity.

2. It is indicated when, in addition to the above, a great degree of ambulation and/or atropine-like action is desirable.

3. It is indicated when a calming, "tiring", "holding down" effect without marked hypotension is required.

4. Varying degrees of sedation and relief from anxiety can be obtained, although these are not determined by the action of the drug alone.

Contraindications:

1. In those patients who present the psychodynamic contraindications we have previously described, and that pertain to any of the tranquillizing drugs,[18, 19, 22, 23] such as patients who interpret any drug as a homosexual or heterosexual seduction, and those patients in whom the transference phenomenon determines panic reactions, body image changes, paranoid thinking, or homosexual panic. It is contraindicated in retarded depressions without agitation, in cases of marked withdrawal and reduction of energy output without agitation or anxiety.

2. In patients in whom the marked atropine-like side effects are contraindicated, or are so disturbing as to be undesirable.

3. In patients in coma because of barbiturates, narcotics, or alcohol, since this drug potentiates their action.

4. In higher doses in the elderly patient to whom proper supervision cannot be given.

5. In patients whose bone marrow is depressed or hypofunctional.

SUMMARY

1. Pacatal is a useful drug in psychiatric conditions for the relief of selected symptoms, provided that it is used in adequate dosage. Proper supervision of the patient is necessary.

2. The drug is useful in any condition where one wishes to diminish energy output, stop overactivity, and calm and sedate the patient in this sense.

3. It is pharmacologically a very active drug with a marked atropine-like action.

4. It has a mild hypnotic effect and is without marked hypotensive action.

5. Patients tend to remain ambulatory to a greater degree than with reserpine and chlorpromazine, but energy output is markedly reduced. Overactivity is controlled, and it makes patients feel calmed and sedated.

6. An atropine-like action is always evident. When marked, it was considered as a side effect, and it can become sufficiently evident to cause considerable discomfort to the patient (see text).

7. It has a relatively poor hypnotic effect for the first few days, so that night-time sedation is sometimes necessary on oral dosage.

8. This drug should be used in adequate dosage and with proper regard for its potent side effects.

9. Patients should be properly supervised while receiving this drug. Supervision should include periodic white cell counts. In these circumstances we do not believe Pacatal to be an unduly dangerous drug.

10. In this series it proved a very useful and beneficial addition to the therapeutic armamentarium of mental illness.

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REFERENCES

1. BOWES, H. A.: *Am. J. Psychiat.*, 113: 530, 1956.
2. BRAUN, M.: *Ibid.*, 113: 838, 1957.
3. BURKITT, E. A. AND RIXON, P. E.: *Brit. M. J.*, 1: 464, 1957.
4. FELDMAN, P. E.: *Am. J. Psychiat.*, 113: 589, 1957.
5. FELDMAN, P. E., BERTONE, J. AND HILDEGART, P.: *Ibid.*, 113: 842, 1957.
6. HORATZ, K.: *Anæsthetist*, 3: 193, 1954.
7. *Idem*: Kaltetechnik, C. S. Muller, Karlsruhe, 1954. pp. 28-31.
8. HORWITT, M. K.: *Science*, 124: 429, 1956.
9. KLEINSORGE, H.: *Arztl. Wchnschr.*, 9: 271, 1954.
10. *Idem*: *Med. Monatsschr.*, No. 7: 760, 1955.
11. KLINE, N. S. AND JACOB, G. M.: *Am. J. Psychiat.*, 112: 63, 1955.
12. KLINE, N. S.: *Ibid.*, 113: 565, 1956.
13. KRZANOWSKI, M. AND ROGERS, M.: *Brit. M. J.*, 1: 463, 1957.
14. MITCHELL, P. H., SYKES, P. AND KING, A.: *Ibid.*, 1: 204, 1957.
15. NIESCHULZ, O., POPENDIKER, K. AND SACK, K. H.: *Arzneimittal-Forsch.*, 4: 232, 1954.
16. PARKER, C. S.: Quoted by Mitchell, P. N., Sykes, P. and King, A. (Ref. 14).
17. SARWER-FONER, G. J. AND OGLE, W.: *Canad. M. A. J.*, 73: 187, 1955.
18. *Idem*: *Canad. Psychiat. A. J.*, 1: 11, 1956.
19. *Idem*: *Canad. M. A. J.*, 74: 526, 1956.
20. SARWER-FONER, G. J. AND KORANYI, E. K.: *Canad. Psychiat. A. J.*, 1: 92, 1956.
21. SARWER-FONER, G. J., KORANYI, E. K. AND DANCEY, T. E.: *Canad. M. A. J.*, 76: 933, 1957.
22. SARWER-FONER, G. J.: The Transference and Non-specific Drug Effects in the Use of the Tranquilizing Drugs in Psychiatry, and Their Influence on Affect, Presented at the Regional Research Meeting of the American Psychiatric Association, Syracuse, N.Y., April 5, 1957. In press, *Am. Psychiat. A. Res. Rep.*
23. *Idem*: *A.M.A. Arch. Neurol. & Psychiat.*, in press.
24. SIMPSON, R. W.: *Brit. M. J.*, 1: 464, 1957.
25. WERENBERG, H.: *Nord. med.*, 54: 1787, 1955.
26. WITTKOWER, E. D. AND LA TENDRESSE, J. D.: *Brit. J. M. Psychol.*, 28: 42, 1955.

RÉSUMÉ

Les auteurs font part des résultats obtenus dans le traitement de malades mentaux dans un établissement psychiatrique libre avec un nouveau produit connu sous le nom commercial de "Pacatal" (*marque déposée*). Ce médicament a son utilité en psychiatrie à condition de l'administrer en dose suffisante et sous une étroite surveillance. On peut s'en servir pour réduire toute dépense inutile d'énergie, arrêter l'hyperactivé, calmer et amortir le malade. Au point de vue pharmacologique, la mépazine est un produit fort actif rappelant l'action de l'atropine; c'est aussi un léger hypnotique sans action hypotensive prononcée. Tout en réduisant l'hyperactivité ce médicament n'a pas la tendance à alourdir le malade comme le font la réserpine et la chlorpromazine. Dans les premiers jours du traitement son effet hypnotique est très peu prononcé de sorte que des sommnifères nocturnes peuvent être requis au début. On doit surveiller l'activité de la mœlle osseuse par une détermination du nombre de globules blancs dans le sang périphérique à des intervalles réguliers, même si le médicament ne semble pas particulièrement toxique à ce point de vue.

A FALLACY IN CLINICAL MEDICINE—VIBRATION SENSE IN THE AGING AND THE AGED*

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IT HAS BEEN our experience to hear neurologists dogmatically state that vibration sense is impaired in the lower limbs in a large percentage of older people. This statement has invariably been based on the usual clinical method of testing vibration with an ordinary tuning fork (128 vibrations per second). It has also been our experience to hear recent graduates of medicine and interns repeat such statements as a definite fact.

REVIEW OF THE LITERATURE

A perusal of some of the leading neurology textbooks on this subject revealed the following statements:

1. Sir Russell Brain[1]—"After the age of fifty the appreciation of vibration may be reduced in normal people."

2. Gordon Holmes[2]—"Acuity of perception diminishes with advancing age, especially in the lower limbs."

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3. Wechsler[3]—"Perception of vibratory sensation in the legs is diminished with advancing age and may be even lost in very old people."

Other textbooks on neurology state similar viewpoints. At first glance the remarks from a variety of sources such as these could be most convincing. However, our experience with aging and chronically ill patients in a large veterans' hospital led us to doubt the soundness of these conclusions about vibration sense. We began to study this problem in 1950 and gradually data have been accumulated which we believe can be analyzed.

Rumpf is credited with introducing the tuning fork in clinical medicine in 1889. He used 14 different types of tuning forks, with vibrations varying between 13 and 1000 per second.

Capt. Symns[4] in 1911 devised a tuning fork with a frequency of 108.75 v.p.s., but with two pieces of steel attached to the upper portion of the fork, so that when the arms of the tuning fork were vibrating a small window was seen between them. When the vibrations of the fork reached a definite amplitude the window disappeared, and at this moment the tuning fork was applied for testing. With this tuning fork, Symns was able to achieve constant frequency and constant amplitude. The Symns tuning fork is a rather bulky and heavy type of instrument, and costs approximately $27.00. In comparison the ordinary tuning fork is much lighter and sells for a fifth of the price.

A more sensitive instrument, known as a pallesthesiometer, was made by Henney for Tilney in 1929. This was further improved in 1936 by Laidlaw and Hamilton, so that they were able to determine vibratory thresholds over different parts of the body in normal and abnormal states. Their instrument was essentially an electrically stimulated oscillating rod; by varying the amplitude of vibration a threshold of perception was determined.

Since then other instruments, somewhat modified, but on the same principle, have been used. Roth in 1941 called his instrument a neurometer, and found that vibration sense in the aged frequently fell to pathological levels, even in the absence of specific detectable disease of the nervous system. He also found that of patients with a past history of head injury with unconsciousness some 50% had impaired vibration sense.

In 1946 Collens, Zilinsky and Boas,[6] using a vibrometer, tested some 100 diabetics with symptoms of neuropathy. Not one had a normal vibration sense in the lower extremities. Of 100 diabetics, without symptoms of neuritis, only 26 gave normal readings in the upper extremities, and four in the lower. Of some 58 juvenile diabetics with no symptoms of neuritis, 43% had impaired vibration sense in the lower extremities. A further report by the same group appeared in 1950, in which they showed that impaired vibration sense in diabetics was more likely to occur in those with proteinuria.

In 1948 Goldblatt,[5] using the same technique as Roth, examined some 200 patients in the age group from 18-45 with venereal or dermatological diseases. He also found that a past history of trauma, with unconsciousness, affected vibration sense in 75% of the patients. Other findings included a depressed vibration sense in early and late lues, as well as in lymphogranuloma venereum and hypothyroidism.

E. C. Gregg, Jr.,[7] in 1951, devised an instrument in which absolute measurement of the vibratory theshold was believed to be obtained. However, he found that in general only subjects of college level intelligence or greater would give consistent data, with small probable error. He also found that drugs, excessive noise, and extremes of temperature and humidity, as well as fatigue, influenced the accuracy of the results.

From the above one can see that although more sensitive instruments have been devised for testing vibration sense more accurately than the tuning fork, various factors have to be taken into account in the interpretation of results. The average physician still uses an ordinary tuning fork in his day-by-day examination of vibration sense.

Vibration Sense and Age

Review of the literature bearing on vibration sense with regard to age has shown a need for more information. In 1928 Pearson[8] noted this same lack of any large study and he was able to find only a few references. These were chiefly European—Egger in 1899, Nydal and Seiffer in 1903. Both reports concluded that there was a diminution in vibration sense with advancing age.

Pearson investigated some 107 patients. Their ages varied between 10 and 90 years, and

40 had a neurological disease, such as Parkinsonism, hemiplegia, or chorea. He used a tuning fork with 128 v.p.s., and tried to induce vibrations with the same force of blow each time. If vibrations were appreciated, the prongs were touched to stop it, and if the reply was simultaneous with the cessation of vibration the fork was struck again and the length of time the vibration was felt was timed with a stop watch. He concluded that adolescents perceived the vibrations best, but decade by decade there was a slight decrease in the sensibility over the lower extremities, and this decrease became striking after the age of 50 years.

One can citicize this work on the basis of:

1. Choice of patients—40 of the 107 patients had a neurological disease, and more than a few were of low mentality, partly acquired from their disease, so that their response to the stimulus and their reliability must be questioned.

2. Because the duration of vibration was used as a criterion, the same force had to be applied to give reliable results. That one could do this over a period of days or weeks in testing different patients is very dubious.

In 1931 Macdonald Critchley[9] in the Goulstonian Lectures delivered before the Royal College of Physicians, London, on "Neurology of Old Age", had this to say about sensory changes: "The outstanding and perhaps the earliest alteration is seen in respect of vibratory sensibility. There is, with advancing years, a progressive impairment of this sensation, leading eventually to a total loss. This vibratory sense may be impaired at the fingers and toes only. Later it is lost at the wrists and ankles, although still present proximally." No data of his own are given but he quotes Dr. Earl at Tooting Bec Asylum as having found a loss of vibratory sense in 20 out of 49 consecutive patients in whom adequate co-operation was possible.

Trevor H. Howell[10] in 1949 reported the results of neurological examinations in 200 apparently healthy Chelsea pensioners ranging in age from 65 to 91. Amongst other things he found that absent vibration sense over the sacrum and lower extremities was not unusual.

Personal Studies of Vibration Sense

Since 1950 we have been able to examine vibration sense in some 1200 patients, whose ages ranged from 17 to 90.

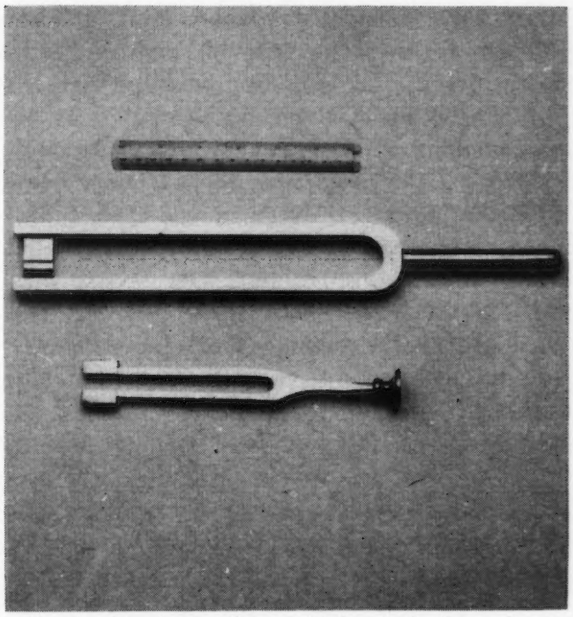

Fig. 1.—The larger Symns tuning fork shown in contrast to the ordinary tuning fork.

Patients selected were either completely well or had organic disease other than involvement of the nervous system. Excluded were: (a) patients with any mental disorder or physical involvement of the nervous system; (b) patients with an illness which might produce neurological complications: for example, patients with diabetes mellitus or alcoholics.

Method of Testing the Patients

The tuning fork used was 8″ (20 cm.) long, with weighted prongs, and a 1″ (2.54 cm.) base. It had a vibration frequency of 128 per second. The tuning fork was struck a blow to set it in vibration. The amount of force used was usually the same, but as the examinations were done over a prolonged period, one could not be certain that the force was absolutely the same. (This error in clinical testing is exactly the same as occurs in day-to-day practice when examining for vibration sense.) As soon as the tuning fork was set in vibration it was immediately applied to the area to be tested. In order to acquaint the patient with the type of sensation he was expected to experience, the test was first performed over the lower end of the radius. Usually the patient described the sensation as buzzing, tingling, vibration, electrical, or a movement. Only such distinct, definite sensations were considered positive. Invariably the response was positive over the lower end of the radius. The test was then repeated over the internal or

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external malleolus of the ankle joint, and the patient was asked to close his eyes and state exactly when the sensation disappeared. By cupping the hand about the tuning fork and then touching it, the vibrations were suddenly stopped. At the same time the examiner could watch the patient. Only an immediate response to the disappearance of the vibration was taken as part of the positive test. The test was repeated 3 times over both ankles. If there was any doubt in the examiner's mind that the patient did not perceive correctly or adequately, or note the time of disappearance, the test was repeated over the tibia, patella, iliac crest or vertebræ. Any impairment in either leg over the malleolus, even though present over the tibia or above, was considered as impaired vibration sensation.

TABLE I.—RESULTS OF TESTING VIBRATION SENSE, SHOWN DECADE BY DECADE ON SOME 1246 PATIENTS: VIBRATION SENSE RELATED TO AGE, USING TUNING FORK (128 V.P.S.)

Age	*Number of patients*	*Number of patients with vibration present*	*% positive*
17 - 39	600	600	100 %
40 - 49	100	100	100 %
50 - 59	208	208	100 %
60 - 69	200	196	98 %
70 - 79	107	98	91.5%
80 and over	31	24	77.4%

The results in Table I indicate that a large majority had an intact vibration sense. Actually, only in those 80 years old or more did the number of cases of impaired vibration sense become significantly high.

On analyzing the histories of the 20 patients with impaired vibration sense, two factors seemed to play a part in causing this. One was the finding of moderate peripheral vascular disease, and the other was the presence of anæmia, either due to iron deficiency or normochromic (none had pernicious anæmia). The level of the hæmoglobin in these cases was invariably 8 grams per cent or less.

CONCLUSION

The vast majority of people, regardless of age, have an intact sense of vibration when tested clinically with the ordinary tuning fork. Where such a sensory impairment is present, one should seek a cause other than aging.

REFERENCES

1. BRAIN, SIR W. RUSSELL: Diseases of the nervous system, 5th ed., Oxford University Press, London, 1955, p. 27.
2. HOLMES, G. M.: Introduction to clinical neurology, 2nd ed., Williams & Wilkins Company, Baltimore, 1952, p. 96.
3. WECHSLER, I. S.: Textbook of clinical neurology, 5th ed., W. B. Saunders Company, Philadelphia, 1943, p. 46.
4. SYMNS, J. L. M.: *Lancet*, 1: 217, 1918.
5. GOLDBLATT, S.: *Arch. Neurol. & Psychiat.*, **59**: 292, 1948.
6. COLLENS, W. S., ZILINSKY, J. D. AND BOAS, L. C.: *Am. J. Med.*, 1: 636, 1946.
7. GREGG, E. C., JR.: *A.M.A. Arch. Neurol. & Psychiat.*, **66**: 403, 1951.
8. PEARSON, G. H. J.: *Arch. Neurol. & Psychiat.*, **20**: 482, 1928.
9. CRITCHLEY, M.: *Lancet*, 1: 1221, 1931.
10. HOWELL, T. H.: *Brit. M. J.*, 1: 56, 1949.

RÉSUMÉ

A la suite de recherches cliniques s'étendant sur plusieurs années au cours desquelles il a examiné des centaines de sujets normaux ou malades, l'auteur en est venu à la conclusion que la perception des vibrations demeure intacte dans la grande majorité des cas, même à un âge avancé. Il s'élève contre les assertions transmises de génération en génération et apparemment sans fondement même si elles sont endossées par les autorités en la matière, voulant que cette perception diminue d'une façon appréciable dès la fin de l'âge mûr. Ses observations personnelles lui ont montré que 77.4% des malades âgés de quatre-vingts ans et plus perçoivent encore les vibrations sans difficulté et que les principales causes qui nuisent à cette perception sont les atteintes vasculaires périphériques et la présence d'anémie ferriprive ou normochromique lorsque l'hémoglobine est en deça de 8.0 g. pour cent. Aucun cas d'anémie de Biermer n'est inclus dans cette série.

CARCINOMA OF THE STOMACH

As a result of a study of 18 five-year survivors after operation for carcinoma of the stomach, Blalock and Ochsner made several suggestions (*Ann. Surg.*, 145: 726, 1957) for possible improvements. The 18 survivors represented 9.4% of 196 patients, of whom only three were not traced.

It is notable that there was a significantly higher survival rate in females, in ulcerative lesions and in lesions of the distal stomach. Radical distal subtotal gastrectomy was the operation done in most of these successes.

The chance of early diagnosis is increased by maintaining a high index of suspicion in patients who harbour a process which might be precancerous. Those lesions clinically benign but cancerous on microscopic examination have the best prognosis. Any physician who advises conservative therapy of any gastric ulcer assumes an unwarranted risk because without serial sections it is impossible to tell whether an ulcer is benign or malignant. Evidence of distant metastases, preferably histologic proof, should be the only factor precluding operability. Approximately 50% of patients with tumours confined to the stomach, treated by resection, survive five years.

Though the survivors had a longer preoperative history than those who died within five years, the longer the disease exists the greater the chance for extension. Earlier diagnosis offers the most logical hope for resectional therapy at a time when it can be curative. The presence of a mass, or its size, the duration of symptoms or the magnitude of the signs and symptoms do not mean that the lesion is not resectable and that a five-year survival may not occur.

AN ANALYSIS OF 192 CONSECUTIVE CASES OF INCISIONAL HERNIA

N. OBNEY,* *Toronto*

AN INCISIONAL HERNIA is one which occurs in the scar of a postoperative wound in the abdominal wall at points other than the inguinal, femoral and umbilical openings. In this series there were 192 cases which comprised 1.42% of 13,544 hernia operations performed at Shouldice Surgery between the years 1946 and 1954 inclusive. The technique for repair of incisional hernia as described in this article was developed by Dr. E. Earle Shouldice.

GENERAL CONSIDERATIONS

(a) *Sex*–Although most textbooks state that incisional hernias are more common in women than in men, the contrary is true in this series. Of the 192 operations 89 (46.6%) were in females and 94 (53.4%) were in males.

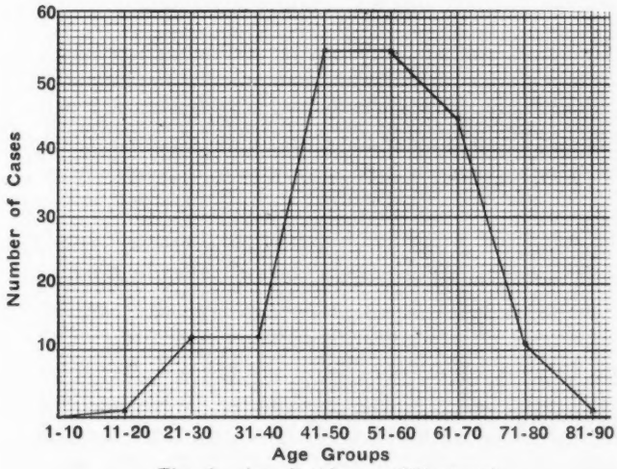

Fig. 1.—Age incidence (192 cases).

(b) *Age*–(Fig. 1)–At the time of operation for incisional hernia the average age in 192 cases was 53.5 years, with a range from 20 to 85 years and a peak incidence between the ages of 41 to 60 years (110 cases or 57.2% of 192). Incisional hernias therefore appear in older age groups possibly because older people have relatively more abdominal operations. Also the muscles in the older patient become more lax and are further weakened by fatty infiltration and degeneration. As the patients become more obese, they consequently become more susceptible to hernia formation.

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(c) *Incisional hernia sites*–Incisional hernias were approximately five times more frequent in the lower abdomen than in the upper abdomen. Of all incisional hernias analyzed, 84.4% appeared in the lower abdomen as compared with 15.6% in the upper abdomen.

TABLE I.—INCISIONAL HERNIA SITES

Right lower quadrant	50.9%
Suprapubic area	24.2%
Midline below umbilicus	9.3%
Right upper quadrant	6.8%
Right paramedian	6.3%
Left paramedian	0.6%
Epigastric	1.9%
	100.0%

(d) *Abdominal operations preceding incisional hernias*–Analysis of abdominal operations preceding incisional hernias revealed that appendectomies, pelvic operations and cholecystectomies were most frequently involved.

TABLE II.—ABDOMINAL OPERATIONS PRECEDING INCISIONAL HERNIA
TOTAL TO DECEMBER 31, 1954 - 192
16 CASES INDEFINITE

Type of operation	*No. of cases*	*Percentage*
Appendectomy	90	51.1
Pelvic	52	29.5
Cholecystectomy	13	7.3
Exploratory laparotomy	8	4.5
Appendectomy and pelvic	4	2.3
Gastrectomy	4	2.3
Suprapubic prostatectomy	2	1.2
Cholecystectomy and pelvic	1	0.6
Diaphragmatic hernia	1	0.6
Nephrectomy	1	0.6
	176	100.0

PREDISPOSING FACTORS

(a) *Obesity*

Of the 192 patients 185 or 96.3% were overweight. Seven or 3.7% of the 192 were not overweight. Six patients of 185 were not asked to lose weight because these patients were operated on in 1946 before weight reduction was instituted. The overweight patients were asked to lose from 5 to 60 lb. One patient actually lost 60 lb. over a period of one year. Average weight at the time of operation was 153.3 lb. Average weight loss was 16.8 lb. Incisional hernias are definitely predisposed to by obesity.

(b) *Wound Infection*

Infection is a great contributing factor in production of incisional hernias. In this series 38.36% of appendectomies, 23.07% of chole-

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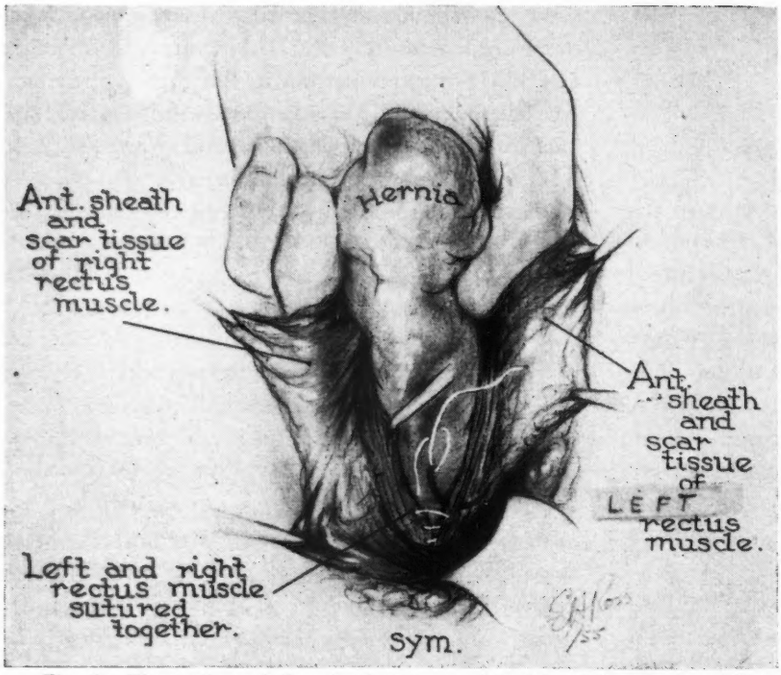

Fig. 2.—Illustration of the simplest type of incisional hernia in midline lower abdomen in the female following a pelvic operation. The narrow-necked, badly scarred, peritoneal sac was removed and the rectus muscles were gently approximated with two lines of running sutures using No. 34 gauge wire.

cystectomies and 13.46% of pelvic operations were infected. The use of modern antibiotics will decrease the incidence of incisional hernias due to sepsis.

(c) *Drainage Tubes*

Drainage of operative wounds is definitely a factor in development of incisional hernias. In this series 34.88% of appendectomies, 7.65% of cholecystectomies and 7.65% of pelvic operations were drained.

(d) *Nerve Damage*

Motor nerve damage to abdominal muscles is frequently encountered in muscle-splitting primary incisions. For example, the intercostal motor nerve to the medial part of the rectus muscle may be damaged, resulting in the atrophy of that portion of the muscle. This leaves a wide space between the recti muscles which is very difficult to close.

ANÆSTHETIC

(a) *Nembutal.*—Each patient received from 1½ to 4½ grains of Nembutal (pentobarbitone), 1½ hours preoperatively. Average amount of Nembutal used was 3.6 grains.

(b) *Demerol.*—Average amount of Demerol used in 151 cases was 5.9 c.c. or 295 mg. (1 c.c. Demerol = 50 mg.). The greatest amount of Demerol used was 13 c.c. or 650 mg. in a 3½-hour operation, given 1 c.c. at 10 to 20 minute intervals. Small doses of 0.5 c.c. or 25 mg. are preferable and may be given at more frequent intervals provided that the patient's respirations are above 8 per minute. In nine cases the respirations actually dropped to 8 per minute.

(c) *Novocaine.*—Average amount of 2% Novocaine (procaine) used was 211 c.c. The largest amount of 2% Novocaine infiltrated was 300 c.c. and the smallest amount was 110 c.c.

(d) *Ether* was supplemented in 20 or 10.4% of 192 cases. Average duration of operation and hence of the anæsthetic was 2.7 hours.

METHOD OF REPAIR

Layer-by-layer repair of abdominal wall offered the greatest security against recurrences. Whenever possible the abdominal layers were dissected out individually and then overlapped as much as possible. When there was so much scar tissue and adhesion that it was impossible to dissect out the layers individually, the whole thickness of the abdominal wall was used. The peritoneum was usually dissected off the posterior surface of the abdominal wall on one side but left attached to the fused and scarred abdominal wall on the other side. The side having the peritoneum attached was then sutured under the side which had the peritoneum dissected off it.

The suture material in this series consisted of stainless steel wire varying in strength from 30 gauge to 34 gauge. On several occasions No. 28 gauge wire was used in the first line of sutures or as temporary retention sutures. No fascia lata or tantalum mesh was ever required. In two cases of recurrent incisional hernia tantalum mesh had to be removed.

Continuous mattress sutures in the first line appeared to be the only means of drawing and holding the muscle and fascial edges together until other lines of sutures could be established

(Fig. 3). From four to six continuous lines of wire sutures were used in the whole repair (Figs. 4 and 5). Meticulous hæmostasis was essential for good results. Dead space between the anterior abdominal wall and the subcutaneous fat was obliterated by multiple continuous wire sutures so that blood and serum could not collect there. Drainage tubes were never used. Michel clips were used in the skin with excellent results. Where it was difficult to bring the musculo-aponeurotic edges together, especially in the upper abdomen, two things were done to facilitate the repair. First, manual pressure was applied on either side of the patient's lower chest and abdominal wall by assistants who were not scrubbed for the operation and were thus able to get their arms and hands beneath the draping sheets. Secondly, each stitch in the first or retention line of sutures was synchronized with the patient's respirations. As the patient inhaled, the sutures were tightened so that the musculo-aponeurotic edges were approximated and overlapped at that time. As the patient exhaled, constant and firm pull was maintained on the sutures so that the stitched areas of the muscle sheaths did not pull apart.

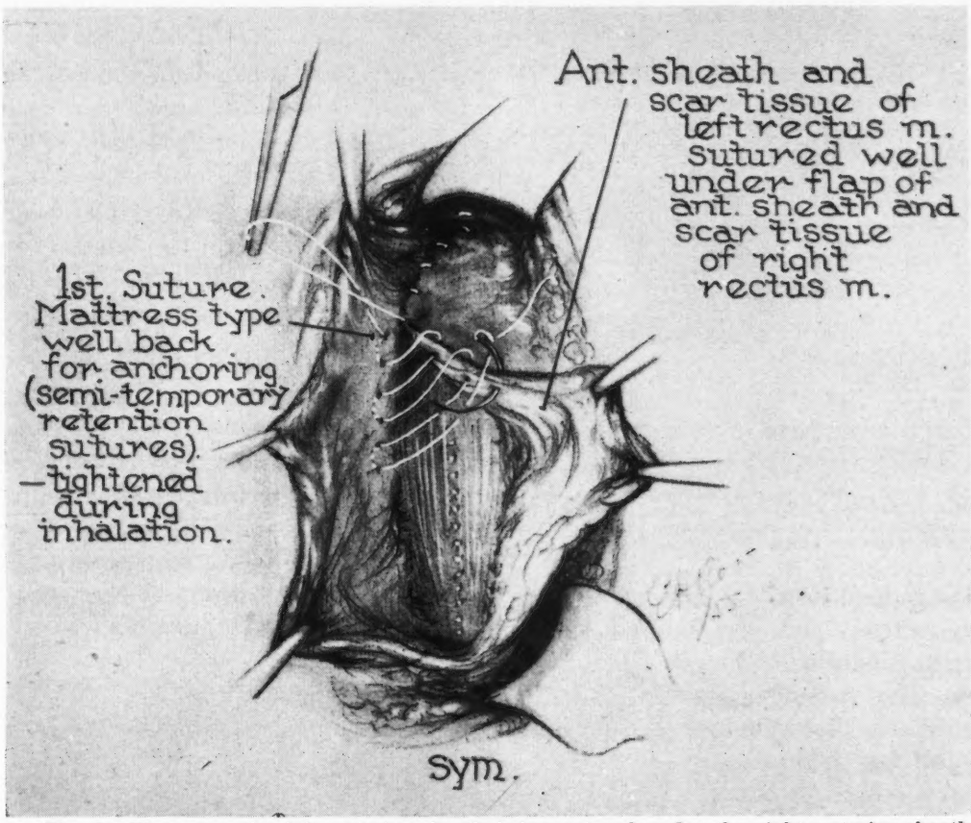

Fig. 3.—Illustrates the left anterior sheath being sutured under the right anterior sheath with first line of mattress sutures using No. 32 gauge wire.

Postoperative Complications (see Table III)

Wound infection was the most formidable complication. Without prophylactic antibiotics or ultra-violet lights in the operating room, 22% of cases became infected. With prophylactic antibiotics as well as ultra-violet lights in the operating room the infection rate was reduced to 3.2%.

There was no mortality in this series of 192 cases. There were no cases of pneumonia, atelectasis, phlebitis or pulmonary embolism.

There was one case of intestinal obstruction due to massive adhesions between the abdominal wall and the small intestines. In the effort to

TABLE III.—POSTOPERATIVE COMPLICATIONS

Infections	
Without prophylactic antibiotics or ultra-violet light	22 %
With prophylactic antibiotics plus ultra-violet light	3.2%
Intestinal obstruction—one case	
There were no cases of:	
(a) Pneumonia	
(b) Atelectasis	
(c) Phlebitis	
(d) Pulmonary embolism	
(e) Mortality	

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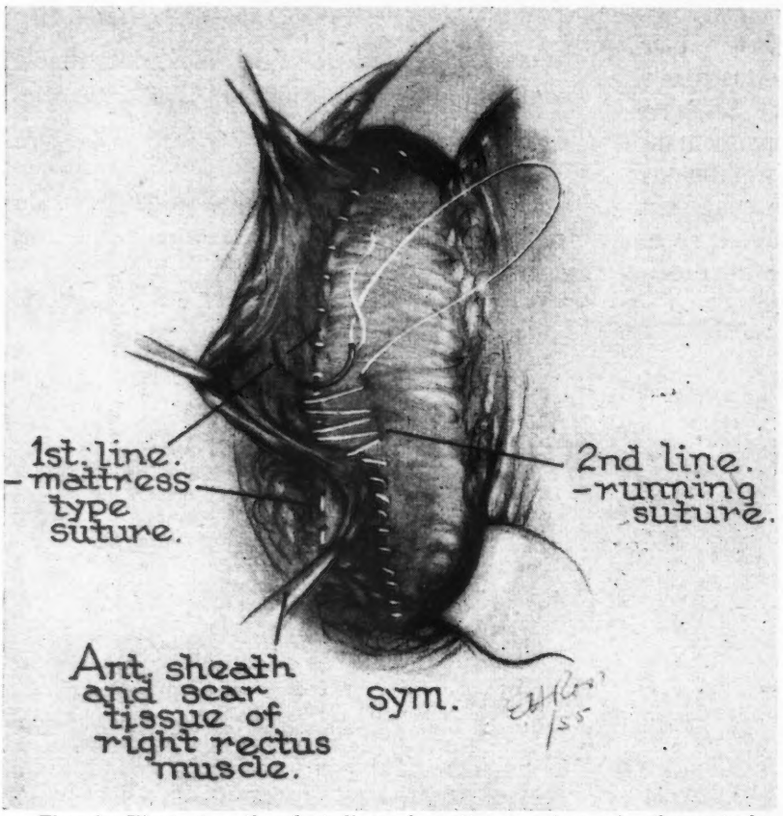

Fig. 4.—Illustrates the first line of mattress sutures in the anterior sheath with a second line of running sutures being inserted, thus overlapping the right rectus sheath over the left rectus sheath.

separate these adhesions the small bowel was inadvertently entered and was sutured longitudinally, further narrowing its small lumen. The patient developed intestinal obstruction during the next few postoperative days and a bowel resection was required to relieve his symptoms. The patient made an uneventful recovery.

With the exception of the above case, all patients made a smooth postoperative recovery without any abdominal or respiratory distress. They were all on full diet, completely ambulatory and discharged from hospital on the third postoperative day.

RECURRENCES

(a) *Our own* – There were only two known recurrences in this series—an incidence of 1%.

One hernia recurred in the upper abdomen and one in the lower abdomen. The former recurrence was due to multiple abdominal incisions and the fact that the dissection was not carried high enough into the right upper quadrant in order to repair the weakness in that area. The second recurrence was due to the dissection not being carried low enough so that the hernia came out just over the pubic bone. In midline lower abdominal hernias, such as the ones that result from a hysterectomy in females, the dissection must be carried right over the pubic bone and the first stitches must be placed well into the ligamentous attachments and periosteum of the bone. The greatest danger of recurrences is at either end of the old incision. Adequate exposure must be obtained so that at either extremity the previous incision can be carefully explored.

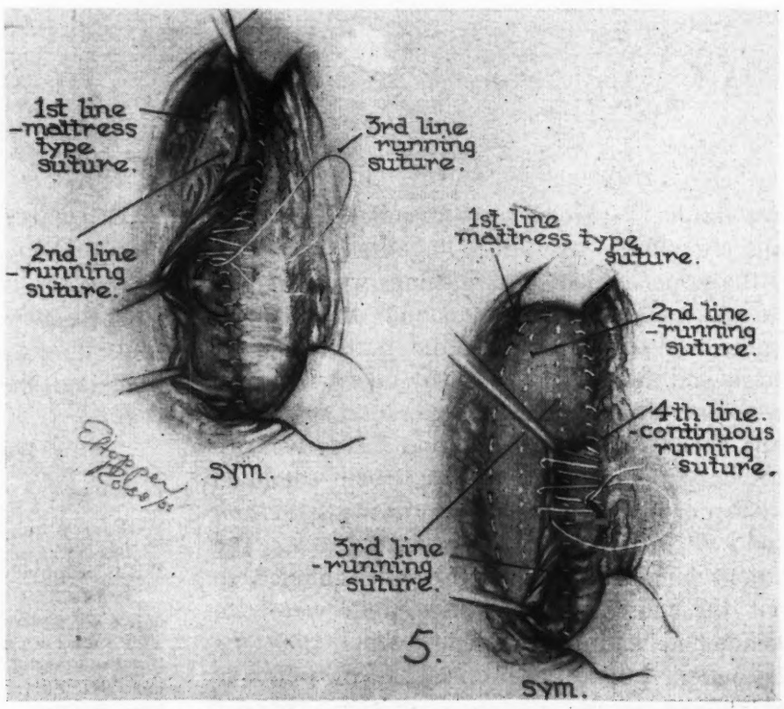

Fig. 5.—Illustrates the final overlapping of anterior sheath with 3rd and 4th lines of running sutures using No. 32 gauge wire.

TABLE IV.—RECURRENT INCISIONAL HERNIAS

A—our own		
No. of recurrences		2
Recurrence rate		1%
B—not our own		
No. of recurrences		22
Recurrence rate		11.4%
Once-recurrent	6 Hysterectomies 5 Appendectomies 1 Prostatectomy	12
Twice-recurrent	4 Hysterectomies 2 Appendectomies 2 Laparotomies	8
Thrice-recurrent	1 Hysterectomy 1 Cholecystectomy	2

(b) *Not our own*—There were 22 (11.4% of 192) recurrent incisional hernias where the original hernia repair was performed by an outside surgeon and subsequently recurred. Some of the recurrences had fascia lata or wire sutures used during the previous operations. There were twelve once-recurrent, eight twice-recurrent and two three-times recurrent incisional hernias.

Of the once-recurrent incisional hernias five followed appendectomies (two McBurney incisions and three right rectus incisions). One recurrence followed a prostatectomy and six followed pelvic operations.

Of the twice-recurrent incisional hernias two followed appendectomies, four followed hysterectomies and two followed other operations unknown to the patient in the region of the umbilicus.

Of the three-times recurrent incisional hernias one followed a cholecystectomy and one followed a hysterectomy.

FOLLOW-UP

The follow-up report on incisional hernia repairs is as of July 1, 1955. The over-all follow-up on patients operated on from one to five years previously was about 58%. Three patients died of causes unrelated to their operations, all with their hernia repairs intact at the time of death. There were only two known recurrences, an incidence of 1%. One recurrence was found at the end of three years and one at the end of five years.

Three methods of follow-up were employed, namely, our staff doctors, other doctors, and letter or telephone. A follow-up letter was sent to each patient on the anniversary of his operation requesting him to report to us for an examination, free of charge. The patient who lived further than 100 miles from Toronto had the privilege of going to his family physician who, on submitting a report to us, received a three-dollar examination fee. Our patients are encouraged to return to us if they have any complaints about their operation. A most cordial relationship is maintained with our patients. Consequently our low recurrence rate is reasonably accurate, as we believe that our patients would report to us if they developed any trouble after their operation.

DISCUSSION

Surgical treatment of incisional hernias is needlessly difficult and dangerous for obese patients. Operation should be postponed until excess weight is lost.

The basic difficulty is a disproportion between the area of the abdominal wall and the volume of abdominal contents. The wall about the hernial ring shrinks when the muscles and fascia shorten because of the separation of their attachments. The muscles atrophy after injury to the nerve supply and lose substance from suppuration and slough. Proper preparation of the patient before operation for incisional hernia is essential. This is particularly true in cases with large defects in the abdominal wall. The examination of the patient with an incisional hernia may be very misleading because excess superficial fat may give an impression that the defect in the abdominal wall is smaller than it actually is.

TABLE V.—FOLLOW-UP TO JULY 1, 1955, ON 192 INCISIONAL HERNIA REPAIRS CARRIED OUT AT SHOULDICE SURGERY FROM JULY 1945 TO DECEMBER 31, 1954

Method of follow-up with number of cases				*Number followed with percentage of possible follow-up*		*No. of recurrences in time of follow-up*		
	Examined by		*Letter*	*Total*		*Checked by doctors*		
Minimum duration of follow-up after operation	*Our staff doctors*	*Other doctors*	*or phone*	*No.*	*Per cent*	*No.*	*Per cent*	
6 months to 1 year	114	8	25	147	70.6%	122	63.5%	0
2 years	67	6	21	94	68.7%	73	53.2%	0
3 years	48	3	17	68	71.5%	51	53.6%	1
4 years	38	1	11	50	75.7%	39	59.0%	0
5 years	16	0	9	25	54.3%	16	34.8%	1

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Postoperative course of the patient is also affected by weight reduction. Increased intra-abdominal pressure has long been recognized as a great danger to the patient's life in the repair of this type of hernia. The importance of weight reduction increases in direct proportion to the amount of intra-abdominal contents protruding through the abdominal wall. In the past some surgeons had to remove considerable portions of intestine and omentum in order to reduce intra-abdominal pressure postoperatively. Failure to reduce this pressure had two undesirable effects on the patient—possible intestinal obstruction and respiratory embarrassment.

Before the incisional hernia is repaired, the defect in the abdominal wall acts as a safety valve by harmlessly dissipating acute increases in intra-abdominal tension. In obese patients intra-abdominal volume is chronically increased from intraperitoneal deposition of fat. When the defect is surgically repaired before excess weight is lost, the sudden increase in intra-abdominal tension is transmitted through the elevated diaphragm to the thoracic contents, with immediate reduction in vital capacity and elevation of venous pressure. The patient may be very ill or die from pulmonary complications. The increased intra-abdominal pressure could also cause intestinal obstruction or paresis further hampering the patient's recovery. Weight reduction in obese patients is therefore imperative before an operation is undertaken.

It is usually a simple matter to cure small incisional hernia protruding through a defect resulting from tube drainage of the abdomen. Similarly, lateral lower abdominal wall incisional hernias do not present great difficulty to the surgeon with a good knowledge of anatomy.

Low lateral abdominal incisional hernias can be made quite difficult, however, if the previous incision was carried medially and involved the linea semilunaris and anterior rectus sheath. A good knowledge of anatomy is required to replace the supporting fascia and muscles into proper anatomical relationship to each other and thus effect a cure. The transversalis and oblique muscles must be repaired and their junction at the edge of the rectus restored in order to obtain a satisfactory result.

Incisional hernias following transverse abdominal wounds were seldom encountered in this series. Where a partial transverse incision was added to a longitudinal one, the resulting hernia was always very difficult to repair. In cases where there has been destruction and atrophy of muscles, especially of the right and left rectus muscles due to motor nerve damage, the operation may be very difficult.

Midline incisional hernias between the chest walls in the upper abdomen or between the pelvic bones in the lower abdomen may present great difficulties to the surgeon. This is especially true in the upper abdomen. In either situation the difficulty may be doubled if a previous repair has failed.

Repair of incisional hernias centrally located and not extending too close to the chest or pelvis does not create so much difficulty as a rule. This is accounted for by the greater ease with which the edges of the hernia can be approximated. There are no bony structures laterally to hinder the making of a narrow waistline, and the edges of the opening can usually be brought together so well that overlapping of the layers can be done, with a permanent and satisfactory result.

Recurrent incisional hernias present an even greater problem because in attempting to repair an incisional hernia too often the surgeon destroys so much of the musculo-aponeurotic edges surrounding the hernia mass that, if his work fails, there is that much less good tissue for a later repair. The surgeon working on a recurrent incisional hernia does not know how much tissue was destroyed in the primary attempt at repair. It is quite possible that the reason a recurrent incisional hernia appears to have had so much tissue destroyed may be the atrophy of the rectus muscle from the original incision. In this type of incisional hernia, if the edges are far apart when the patient tenses the abdominal muscles, one can be almost certain that one is dealing with the last and most difficult type of all abdominal hernias.

Proper preparation of the patient by weight reduction before operation and strong urging to keep the weight down afterwards has made possible successful results even in extremely difficult incisional hernias.

SUMMARY

A series of 192 incisional hernias is presented. The method of anæsthesia, repair and the results of repair are discussed.

CONCLUSIONS

1. Incisional hernias can be successfully repaired without the use of material such as wire mesh or fascia lata provided the patients lose sufficient weight if they are overweight.

2. Age or physical condition is not a contra-indication with the method of anæsthesia used. There were no cases of postoperative shock.

3. Strong, mono-filament, non-absorbable suture material, such as wire, is essential.

RÉSUMÉ

L'auteur présente une série de 192 cas d'éventration post-opératoire tirée des archives d'une clinique hautement spécialisée dans le traitement des hernies. Le plus grand nombre des malades étaient âgés de 41 à 60 ans. Cette période de la vie est celle où l'on subit le plus grand nombre d'opérations abdominales où la musculature est souvent d'assez mauvaise qualité et où l'obésité prédomine. Contrairement à ce que l'on a déjà rapporté ailleurs, le nombre d'hommes de cette série était plus élevé que le nombre de femmes. Les lésions intéressant les quadrants inférieurs abdominaux étaient cinq fois plus nombreuses que celles des quadrants supérieurs. Parmi les facteurs prédisposant à ce genre de hernie, l'obésité vient en premier lieu: 96.3% des patients de cette série étaient obèses. La présence d'infection post-opératoire nécessitant un drainage vient comme deuxième cause. Enfin l'atrophie musculaire causée par la section ou le traumatisme des nerfs moteurs périphériques contribue au relâchement des tissus.

La technique opératoire est basée sur la suture des tissus plan par plan, et avec l'emploi de fil d'acier inoxydable, offre ainsi les meilleurs chances de succès. Il n'est pas nécessaire de recourir à l'aponévrose fémorale ou à la maille de tantale. Afin d'éviter de poser un drain il importe d'avoir une hémostase parfaite. Les agrafes de Michel font très bien pour la peau. La principale complication post-opératoire des cas rapportés ci-haut fut l'infection; on la réduisit considérablement grâce à l'emploi d'antibiotiques et de lumière ultra-violette dans la salle d'opération. On n'eut à déplorer aucune mortalité et tous les malades reçurent leur congé dans la troisième journée post-opératoire. Il n'y eut que deux récidives dans tout le groupe. Chez les obèses porteurs d'éventration, il n'existe aucune gêne à la respiration avant l'opération, mais une fois que les tissus sont rapprochés la tension intra-abdominale augmente à tel point que le diaphragme est poussé vers le haut et diminue les excursions respiratoires. Une cure d'amaigrissement forme donc une mesure pré-opératoire essentielle.

POSTURAL DEPENDENCY TREATMENT IN CAVERNOUS PULMONARY TUBERCULOSIS*

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SINCE THE WORK OF Dillwyn E. Thomas of Sully Hospital in South Wales, first reported in 1947,[1] postural dependency treatment of pulmonary tuberculosis has found increasing acceptance throughout the British Isles[2-5] and parts of Continental Europe.[6] In its development it has also been known as postural recumbency, postural reduction, postural retention and postural blockage. This report will deal with experience with this form of treatment as used in the sanatoria of the Saskatchewan Anti-Tuberculosis League during the past three years. Although the number of cases is limited to some forty, the results appear to be sufficiently encouraging to warrant a report at the present time.

TECHNIQUE

Postural dependency treatment is bed rest with the patient so positioned that the affected lung part is as low as possible. The location of the cavity is determined by postero-anterior (PA) and lateral chest films and by AP and lateral tomography. The patient is then positioned so that the segment containing the cavity is as low as possible in relation to the rest of the thorax. To achieve this the foot of the bed is elevated and the patient so rotated as to place the cavity in the lowest position. This position is maintained by sandbags or pillows.

Fig. 1 shows diagrammatically the principles of the positioning for a cavity in the posterior segment of the right upper lobe. The foot of the bed has been raised 9 to 12 inches (22.5-30 cm.) and the patient turned sideways 35° from the supine with his diseased side down. It can be seen that the cavity is as low as possible.

Cavitation in the superior segment of the lower lobe is treated in the same position.

If the cavity is in the apical segment of the upper lobe or laterally situated, the foot of the bed is again raised up to 12 inches but the patient should now lie entirely on the diseased side, that is, turned 90° from the supine position.

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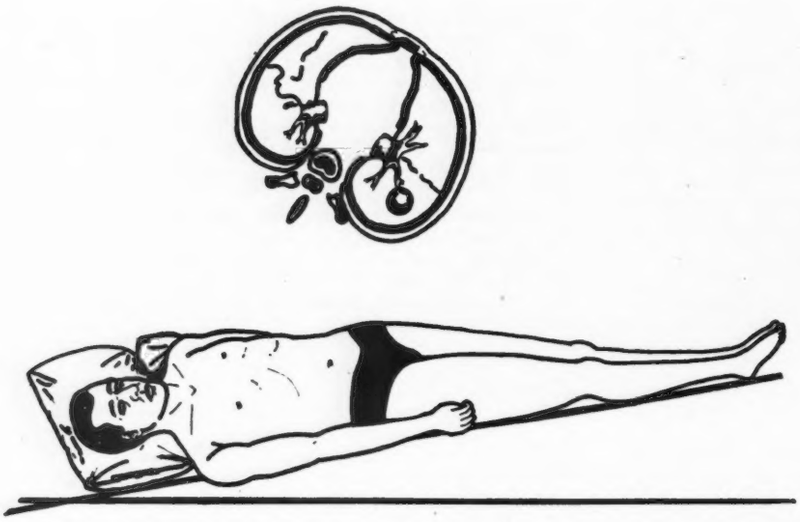

Fig. 1.—Positioning for a cavity in the posterior segment of the right upper lobe. Note (1) the elevation of the foot of the bed and (2) the rotation of 35° toward the right side (see inset).

Anterior cavities are relatively rare but if they are to be treated by posture, the patient must be maintained in the prone position with the foot of the bed raised and the better side of the patient rotated up 35° from the horizontal.

In the case of bilateral cavities, rotation of the patient to one side or the other is of course inadvisable, and postural treatment is carried out by elevation of the foot of the bed with the patient resting in the supine position.

Postural treatment is always begun by strict maintenance of the supine position in the case of posterior cavities, or the prone position for the rare anterior locations. The complete cooperation of the patient as well as the nursing staff is essential. Within a short time the patient learns to relax and becomes used to resting in a required position. As soon as he is accustomed to this immobilization, the foot of the bed is raised to the desired level by three-inch increments at three-day intervals. Then the patient is rotated to the required angle. He is instructed to lie so that only his head and neck are on the pillow. It is useless to elevate the foot of the bed if the patient slides toward the headboard so that his shoulders become raised.

It has not been found necessary to maintain postural dependency in as rigid a manner as done at Sully Hospital.[7] There the patient had a plaster shell made in which he was nursed in almost the same way as patients with spinal lesions. Satisfactory results have been obtained when the position of the patient was maintained only by pillows or sandbags. Interruptions of posture are permitted for bathroom purposes once a day. Admittedly the maintenance of proper posture requires a certain tenacity on the part of the patient, but most of them become enthusiastic about the treatment when their rapid radiological improvement is demonstrated, and they readily accept the necessary discomfort and restraint. The length of time for which posture has to be maintained depends upon its effect on the cavity. Maximum shrinkage of the cavity can usually be achieved in two to four months.

Postural treatment in cavernous disease is best begun simultaneously with drug therapy. The persistently open cavity is recognized as an important stumbling block in today's chemotherapy of tuberculosis.[8] Since posture procures rapid cavity closure it enhances and maintains the beneficial effects of drug treatment. In the last few years reports have appeared describing the transformation of cavities into giant cysts after long-term chemotherapy.[9] It is felt that these cysts can be avoided if postural treatment is applied simultaneously with chemotherapy.

INDICATIONS

Each patient with unilateral cavernous pulmonary tuberculosis should have postural treatment as soon as drug therapy is commenced. In bilateral cavitation, of course, posture can be of benefit only when the cavities are either all anterior or all posterior.

Posture is instituted prior to pulmonary resection for the following reasons. First, when cavities are closed or inspissated, there is less danger of dissemination or of a spill-over during the operation. Secondly, the involved part of the lung contracts under posture and the inevitable post-resectional overexpansion of the remaining lung[10] has already been partially obtained in the preoperative period. Thirdly, the method provides a good function test for the contralateral lung and the remaining part of the diseased lung, since lesions of doubtful stability will reveal their true character preoperatively when exposed to the stress of overexpansion.

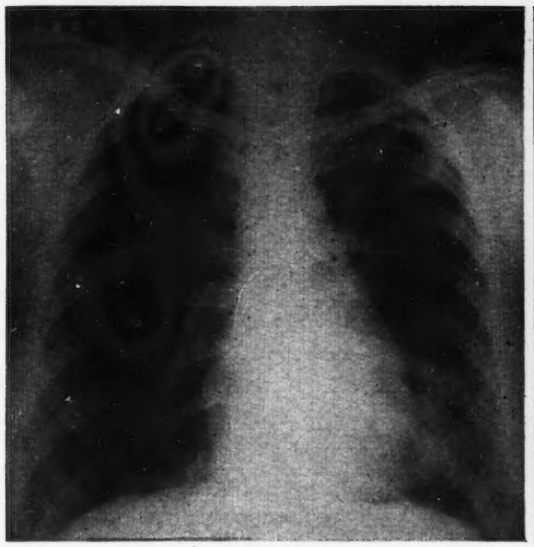

Fig. 2

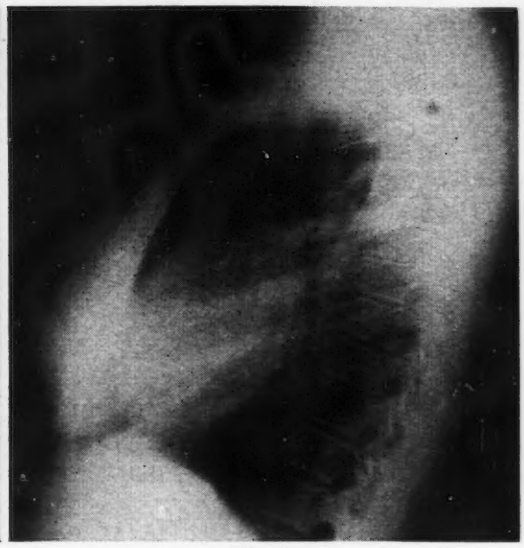

Fig. 3

Fig. 2 (Case 1).—The admission chest film shows a medium-sized cavity in the left upper zone. **Fig. 3** (Case 1).—A left lateral view localizes the cavity in the apico-posterior segment of the left upper lobe.

Postural treatment is regarded mainly as a preparation for surgical measures. However, patients who appear unable to tolerate or who refuse an operation also benefit from the closing of an open cavity. Residual cavities under thoracoplasties show excellent response to postural dependency since the thoracoplasty has already achieved a marked relaxation of the underlying lung. Even patients with persistently open cavities despite long-term chemotherapy often show surprisingly good results.

CONTRAINDICATIONS

The only important contraindication to postural dependency treatment is marked tuberculous endobronchitis in the visible part of the tracheo-bronchial tree at bronchoscopy. There is danger of producing complete atelectasis rather than a selective relaxation if the main bronchus is stenosed and shows a significant degree of endobronchitis.

COMPLICATIONS

The most frequently encountered side effects of postural treatment are disturbances of the gastro-intestinal tract. In the first two weeks after elevation of the foot of the bed, episodes of nausea and anorexia occurred in a few pa-

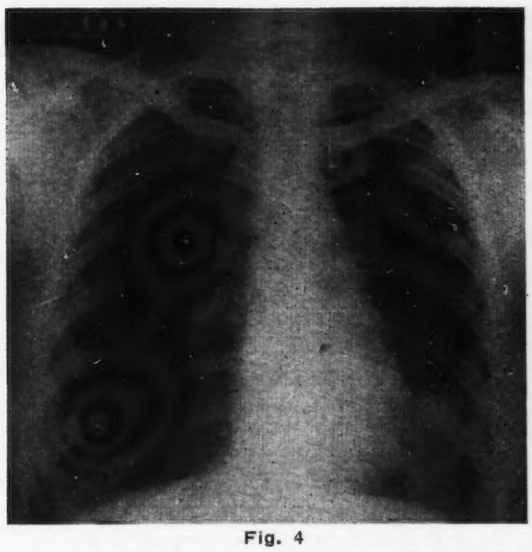

Fig. 4

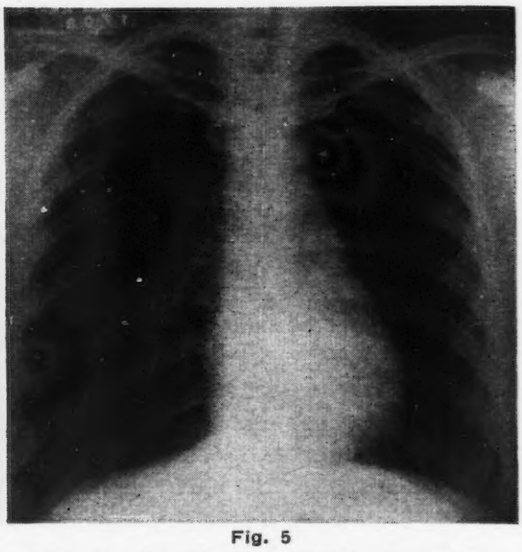

Fig. 5

Fig. 4 (Case 1).—After 11 weeks of postural treatment and combined chemotherapy. Planigrams no longer show evidence of excavation. **Fig. 5** (Case 1).—A review film taken one year after discharge from the sanatorium.

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tients. However, in none of these patients was interruption of treatment necessary.

In two patients a "frozen shoulder" developed which could be corrected by physiotherapy. The patients since then have been instructed to move and use their shoulder joints.

Probably due to the fact that all posture patients are permitted to get up once a day for a period of 15 minutes, circulatory complications in the lower limbs, as noted by Breathnach and Quinn,[11] have not been observed.

Posture had to be discontinued in one patient with bilateral renal tuberculosis because of increasing frequency and pain on micturition.

RESULTS

The number of patients treated by postural dependency in this series is limited to forty-odd. It is a very diversified group with regard to age, type of disease and previous treatment. Most have had preceding long-term chemotherapy in various forms. Some have had operative procedures and had remained hospitalized or were readmitted because of positive sputum. In only a small number was posture instituted as a primary therapeutic measure. The limited number of patients, as well as the lack of a control group, does not permit a statistical evaluation.

There were only two cases in the series in which the cavities were not closed. In one of these postural treatment was discontinued because of an increase in symptoms of renal tuberculosis. The other patient discharged himself from the sanatorium after the cavity had been reduced to one-third of its size at the beginning of treatment despite the fact that it had persisted for almost twenty years.

CASE REPORTS

The following cases are a representative cross section of the material and results.

CASE 1.—E.N., a 30-year-old white housewife, was admitted as a result of a hospital admission film taken when she was confined at the end of May 1953. Her sputum was bloodstained at the beginning of May 1953 and was positive for acid-fast bacilli on admission. Postural treatment and combined chemotherapy were instituted and resulted in rapid closure of the cavity. This patient was hospitalized from June 1, 1953, until May 11, 1954.

CASE 2.—M.W., a 24-year-old Indian woman, was first admitted to the sanatorium in 1944, and had a right phrenic crush and a six-rib thoracoplasty in 1946. She was asymptomatic until the spring of 1952 when she noticed increasing productive cough which was followed by a severe hæmoptysis in October 1952. Her sputum became negative after three months' treatment. The patient left the sanatorium against advice in October 1953, after 11 months' treatment. The cavity remained closed as seen on a review film taken 17 months after discharge. This case shows a relatively rapid and stable closure of a cavity in a patient in whom surgical intervention was considered inadvisable.

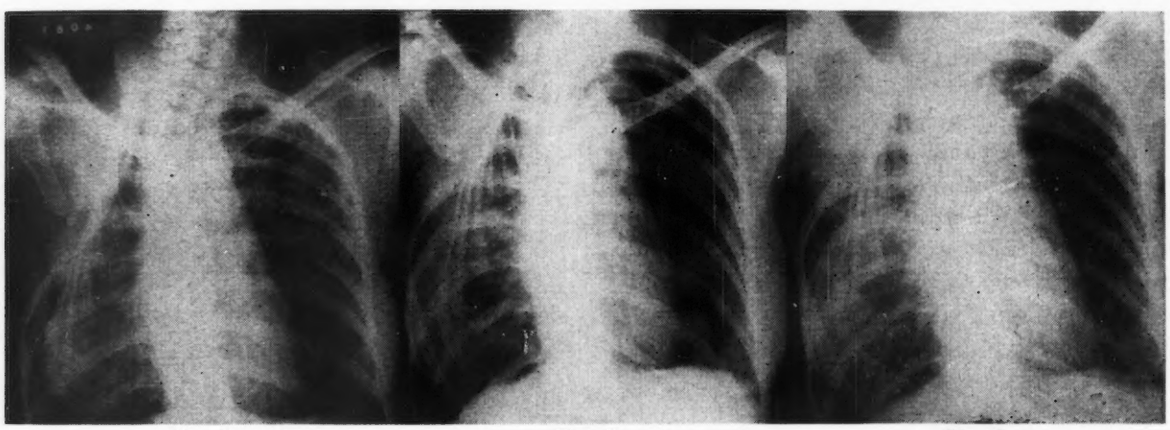

Fig. 6 Fig. 7 Fig. 8

Fig. 6 (Case 2).—Admission chest film showing a thin-walled cavity in the left apex. Fig. 7 (Case 2).—Residual density in place of the cavity after three months' treatment. Fig. 8 (Case 2).—Review film 17 months after self discharge.

CASE 3.—P.O., a 26-year-old white housewife, was admitted in December 1953, with bilateral renal tuberculosis and a history of productive cough for four years. The admission chest film (Fig. 9) shows multiple excavations and a pleural effusion on the right and a giant cavity in the left apex. The plan of treatment was to close the left apical cavity in preparation for a right pleuropneumonectomy. In view of the bilateral cavitation the patient was postured in the supine position and received combined chemotherapy. After three months' treatment the left apical cavity was replaced by an irregular density (Fig. 10). Later on the patient did not consent to operation and left the sanatorium after

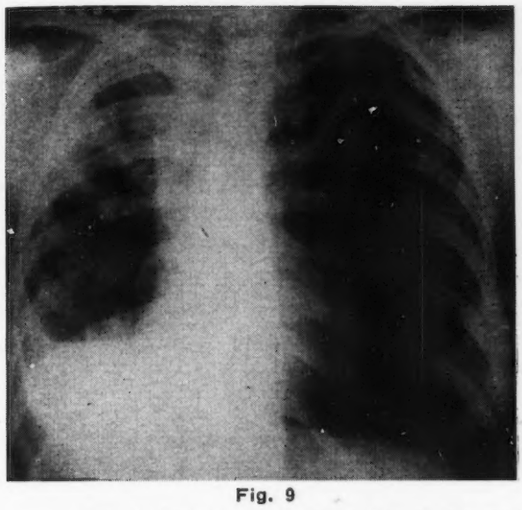

Fig. 9

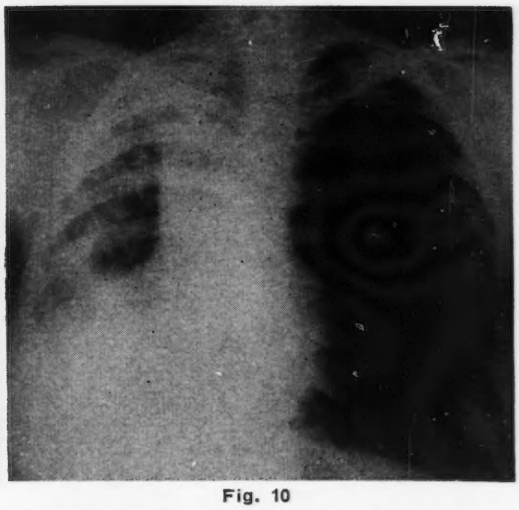

Fig. 10

Fig. 9 (Case 3).—Admission film shows multiple cavities and a pleural effusion on the right and a giant cavity in the left apex. Fig. 10 (Case 3).—About three months later the left apical cavity is replaced by an irregular density.

one year's treatment. Later review films were reported to show no reopening of the left apical cavity.

CASE 4.—S.E., a 46-year-old white male, was admitted to the sanatorium in May 1952. At that time his chest film showed a destroyed left upper lobe and a small cavity in the right mid zone. The latter increased in size despite combined chemotherapy and reached its maximum size in March 1954 (Fig. 13). A pneumoperitoneum was then induced and maintained until the end of October 1954, without any noticeable effect (Figs. 14 and 15). The sputum was heavily positive microscopically but bacilli failed to grow on culture and the degree of drug resistance could not be determined. Postural treatment for the cavity in the superior segment of the right lower lobe was begun in November 1954. Five months afterwards the cavity was replaced by a small oval density (Fig. 17). The plan of treatment in this case was to stabilize the right lung in order to perform a left pneumonectomy. A left pleuropneumonectomy was done in December 1955, followed later by a left thoracoplasty.

This case illustrates that a patient, repeatedly rejected for surgical intervention because of bilateral cavernous disease, can be brought into an operable condition despite apparent evidence of drug resistance.

CASE 5.—W.H. was a 20-year-old white male whose pulmonary tuberculosis was discovered in October 1952. The admission chest film showed a large tension cavity in the right apex and nodular lesions scattered throughout the right mid zone. Combined chemotherapy and postural treatment were initiated simultaneously at the beginning of November 1952. Marked shrinkage of the cavity was noted after three months. This conservative management was maintained for one year. Residual densities were

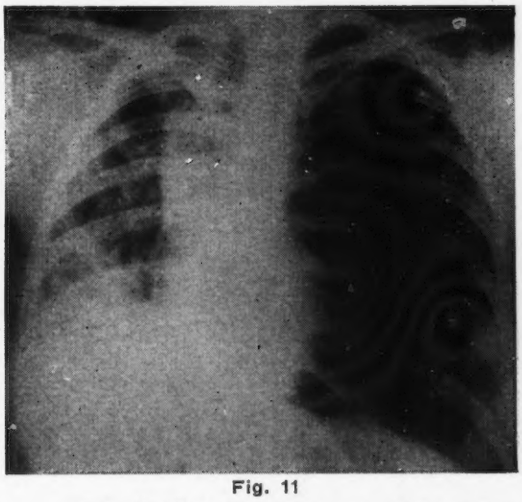

Fig. 11

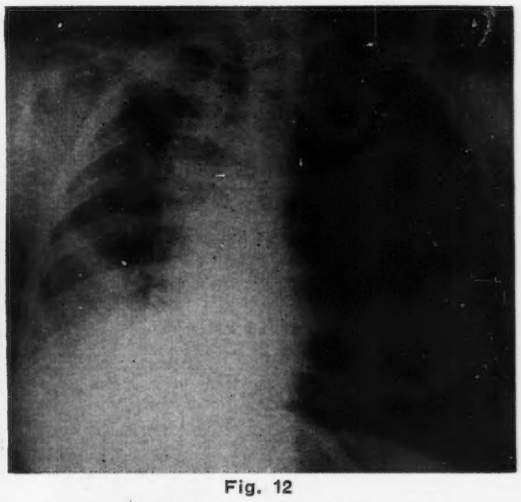

Fig. 12

Fig. 11 (Case 3).—After one year's postural treatment and chemotherapy. Patient did not consent to a right pleuropneumonectomy, and left the sanatorium. Fig. 12 (Case 3).—A review film 15 months after the beginning of treatment. The left apical cavity remained closed.

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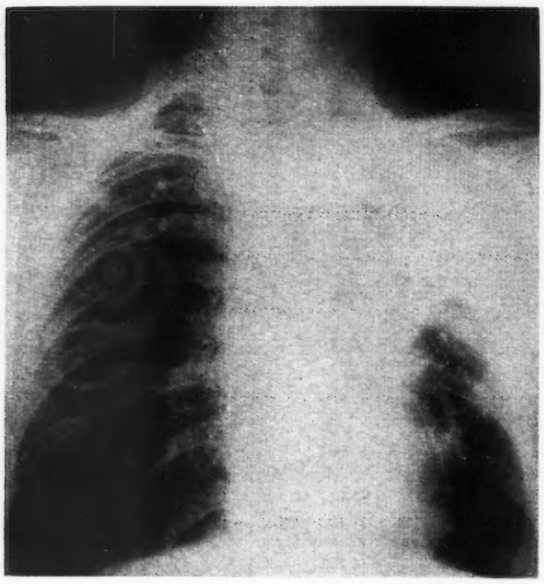

Fig. 13 (Case 4).—Chest film before pneumoperitoneum.

still seen in October 1953. A right upper lobectomy was performed in April 1954, after a preliminary thoracoplasty in March 1954.

DISCUSSION

The aim of postural treatment is to place the cavitated lung part in as dependent a position as possible. The following observations show that by this procedure a marked "deflation" of the dependent lung part occurs with simultaneous reduction in volume. This effect is elucidated by Fig. 24.

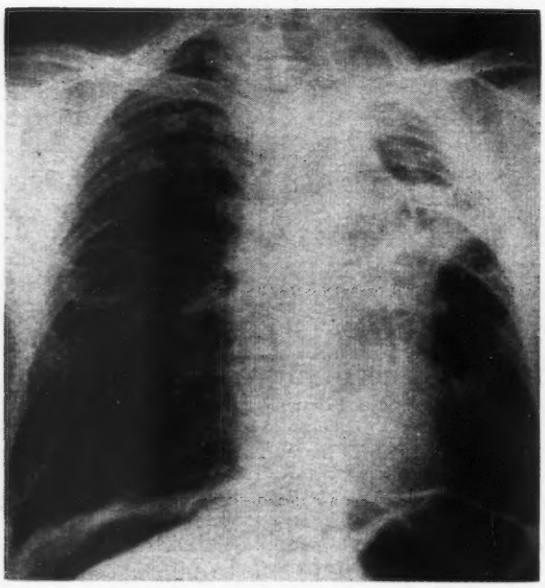

Fig. 14 (Case 4).—Cavity in right mid zone unchanged after seven months' pneumoperitoneum.

In the lateral decubitus the mediastinum becomes displaced towards the lower hemithorax and the lower hemidiaphragm is raised. This elevation is almost as high as in normal expiration and the lower lung appears radiologically more dense, probably due to an increase in blood volume. The upper hemithorax undergoes opposite changes, namely, the upper hemidiaphragm is displaced downwards to the level of a deep inspiration and the upper lung is more radiolucent. In other words, the lower lung assumes a smaller volume and that of the upper lung increases.[12] These observations seem to suggest that the effect of posture is largely mechanical in that the lower lung or lung part is more

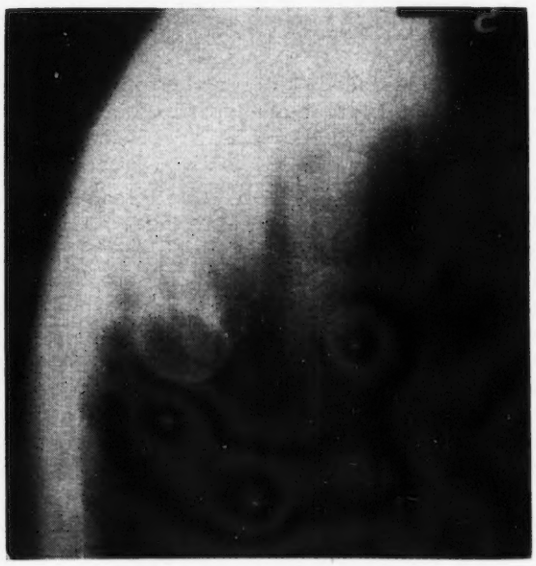

Fig. 15 (Case 4).—The cavity is situated in the superior segment of the right lower lobe.

or less permanently in an expiratory state, and a concentric relaxation is obtained.

Bronchospirometric investigations[12-14] in the lateral decubitus immediately after this position is assumed show an increased oxygen uptake in the dependent lung, decreased functional residual capacity and a slightly increased minute volume. In other words the total volume of the dependent lung is reduced but it works more efficiently. No references could be found to investigations on the dependent lung after long-term decubitus. If a lateral decubitus has been maintained over a longer period, the elevation of the diaphragm of the dependent hemithorax as well as the mediastinal shift seem to persist for a time even after resumption of normal posture.

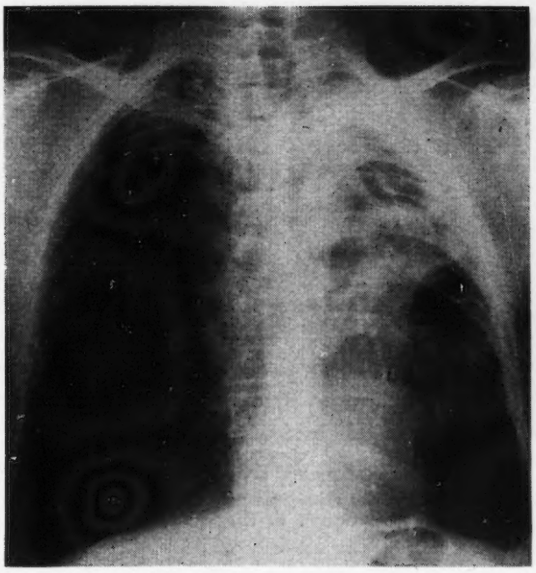

Fig. 16 (Case 4).—After six weeks' posture. The right cavity is smaller and shows a fluid level.

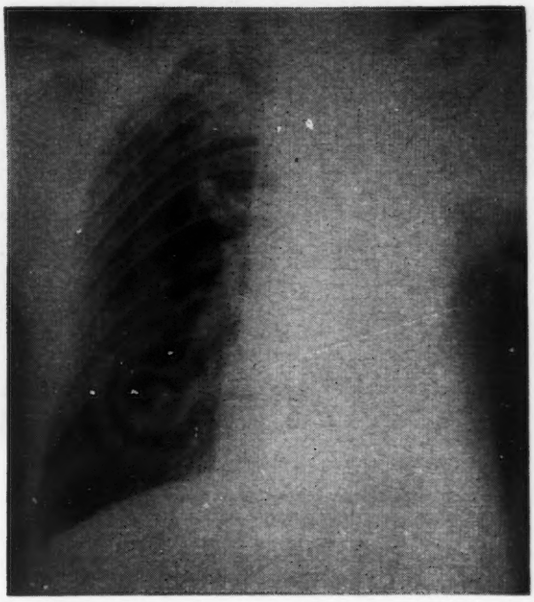

Fig. 18 (Case 4).—Six months after the left pleuropneumonectomy.

This would indicate that there is an alteration in the compliance of the dependent lung.

Dillwyn Thomas's original observation of changes in the size of a cavity—shrinking when in a dependent position and increasing in size rapidly when the patient is positioned so that the same cavity is in an uppermost position — would suggest that postural dependency eliminates the check-valve at the bronchocavitary junction.[15]

The majority of reports assume an actual closure of the bronchial orifice due to the state of "deflation" of the dependent lung. However, this view is challenged by Breathnach and Quinn,[11] who postulate that posture produces a patent bronchial orifice by removing it from the cavity floor, thus initiating its closure by "open healing".

THE ROLE OF CHEMOTHERAPY

All patients in this series have either had chemotherapy before the commencement of postural treatment or received it simultaneously. The few reports available with control groups of patients on posture alone without chemotherapy[11] ascribe an enhancing effect to chemotherapy inasmuch as sputum conversion and cavity closure may be achieved sooner. How-

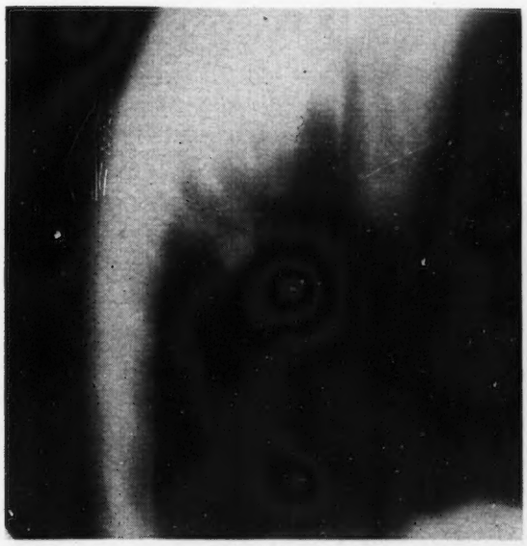

Fig. 17 (Case 4).—After five months' posture. The cavity in the superior segment of the right lower lobe presents itself as a round opacity on lateral planigrams—an inspissated cavity.

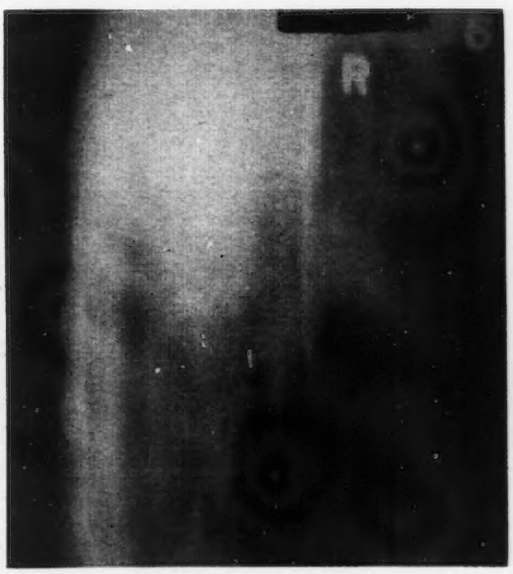

Fig. 19 (Case 4).—Right lateral planigrams show the round opacity replaced by a stellate scar.

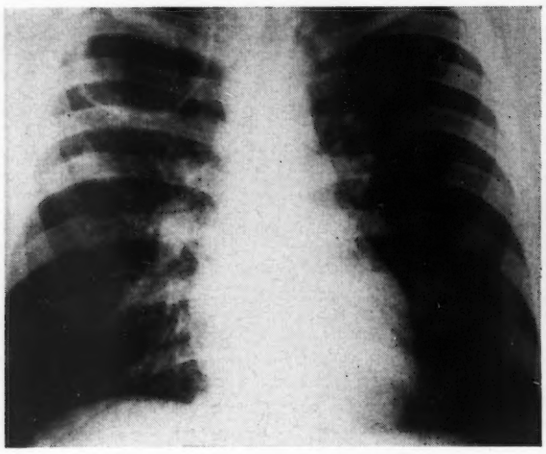

Fig. 20

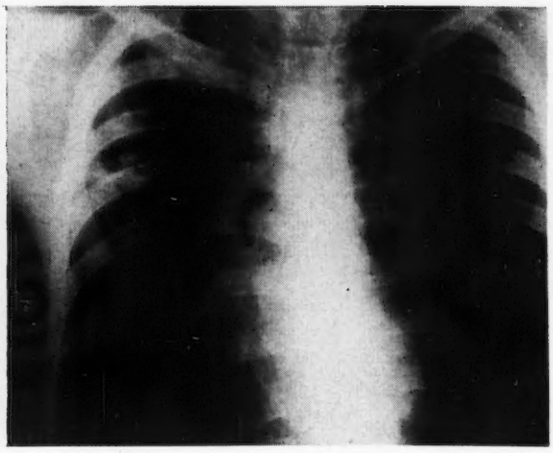

Fig. 21

Fig. 20 (Case 5).—Admission films showing a tension cavity in the right apex and nodular lesions throughout the right mid zone. **Fig. 21** (Case 5).—Marked reduction in the size of the cavity after three months' treatment.

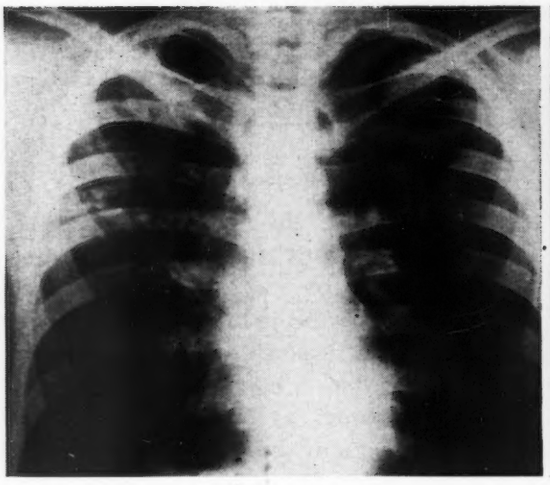

Fig. 22

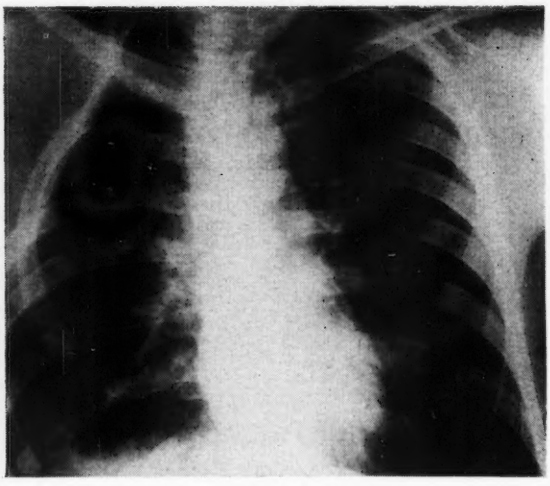

Fig. 23

Fig. 22 (Case 5).—After six months' treatment the cavity is replaced by a stellate scar formation. **Fig. 23** (Case 5).—Postoperative result.

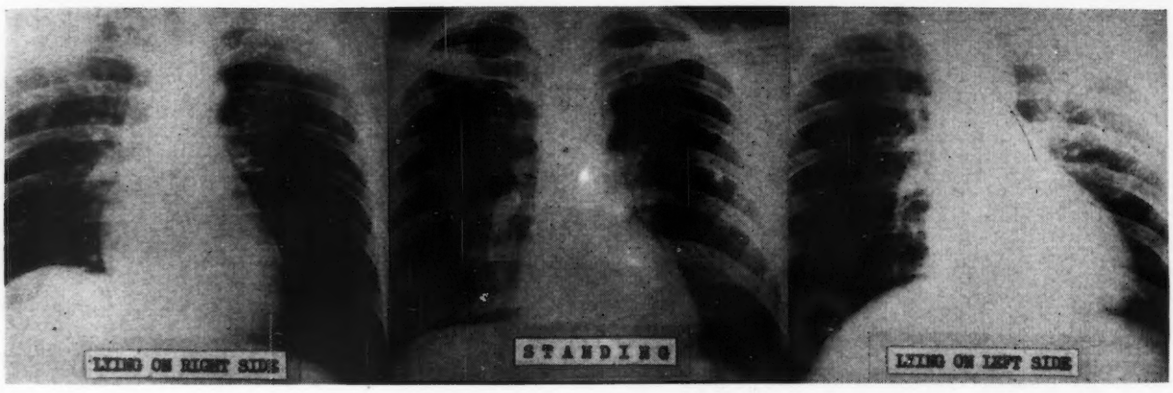

Fig. 24.—See text for explanation.

ever, the reported rate of cavity closure by chemotherapy alone ranges from 35% to 79%.[16] It is felt that in combination with postural treatment this rate can be considerably increased.

Long and intensive chemotherapy in some cases had no marked effect on cavities that were subsequently closed by postural treatment.

CONCLUSION

In conclusion it is felt that postural dependency treatment has an indispensable place in the management of cavernous pulmonary tuberculosis.

In combination with chemotherapy it prevents residual cystic changes by rapid cavity closure and thereby also the emergence of drug resistance.

As a preoperative measure posture reduces the surgical risk. Finally it may bring about improvement and cavity closure in cases which appear beyond the scope of surgical intervention.

In as serious a condition as cavernous tuberculosis all possible therapeutic measures should be employed. The slight inconvenience of postural treatment is more than compensated by its safety and beneficial effects.

SUMMARY

The experience of applying postural dependency treatment to some 40 patients with cavernous pulmonary tuberculosis is reported.

In this treatment the patient maintains bed rest in such a position that the cavitation is dependent in relation to the rest of the lung, a position achieved in most cases by elevation of the foot of the bed and rotation of the body. The underlying parts of the lung assume a state of deflation with ensuing concentric relaxation of the cavitated area. Reduction in the size of the cavity is rapid and closure may be achieved in two to four months.

Concomitant chemotherapy is routine, and by rapid cavity closure the hazards of drug resistance and cystic changes are reduced.

The method of treatment carries no risks and is applicable in all cases of cavitary pulmonary tuberculosis, except (1) where multiple cavities are not in analogous segments or (2) when stenosing endobronchitis is seen at bronchoscopy.

Postural dependency therapy is particularly useful preparatory to surgical procedures but in cases where operation is not advisable it is also of benefit.

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REFERENCES

1. THOMAS, D. E.: *Tubercle*, 29: 216, 1948.
2. BARLOW, D.: *Ibid.*, 32: 186, 1951.
3. DESHMUKH, M. D. AND WILLIAMS, E. H.: *Ibid.*, 32: 240, 1951.
4. ASLETT, E. AND ERIN, L.: *Ibid.*, 33: 206, 1952.
5. LYONS, J. P.: *Ibid.*, 34: 87, 1953.
6. HENSCHEL, E. O.: *Schweiz. Ztschr. Tuberk.*, 10: 394, 1953.
7. THOMPSON, H. T., SAVAGE, T. AND ROSSER, T. H. L.: *Thorax*, 9: 1, 1954.
8. RUSSELL, W. F., JR., *et al.*: *Am. Rev. Tuberc.*, 71: 441, 1955.
9. TCHERTOKOFF, I. G. AND BURASCANO, J. J.: *Bull. Sea View Hosp.*, 15: 113, 1955.
10. WALLACE, J. E. AND PILLMAN, R.: *Thorax*, 11: 149, 1956.
11. BREATHNACH, C. S. AND QUINN, K. J.: *Tubercle*, 36: 362, 1955.
12. VACCAREZZA, R. F. *et al.*: *Dis. Chest*, 9: 95, 1943.
13. ROTHSTEIN, E. *et al.*: *J. Thoracic Surg.*, 19: 821, 1950.
14. SVANBERG, L.: "Les Bronches", 5: 1, 1955.
15. CORYLLOS, P. N.: Clinical tuberculosis, P. Goldberg, F. A. Davis, Philadelphia, 4th ed., 1944, p. 183.
16. ROSS, J. D. AND KAY, D. T.: *Thorax*, 11: 1, 1956.

RÉSUMÉ

L'auteur rapporte les résultats du traitement par repos postural dans plus de 40 cas de tuberculose pulmonaire caverneuse.

Cette cure de repos postural est obtenue en plaçant le patient dans une position dans laquelle le segment ou le lobe pulmonaire contenant la cavité se trouve au point le plus déclive. Cette position s'obtient en élevant le pied du lit et en tournant le malade de façon que la cavité soit au point le plus bas du thorax. Ceci est obtenu en étayant le malade avec des coussins ou sacs de sable.

Il est généralement reconnu que les cavités pulmonaires restent béantes à cause d'un mécanisme de valve qui existe à la jonction de la cavité et de la bronche de drainage; la méthode suggérée par l'auteur empêche probablement l'action de cette valve en favorisant un état presque permanent de détente du poumon par un relâchement concentrique du poumon.

Le diamètre de la cavité diminue rapidement et la résolution radiologique s'obtient après deux à quatre mois de ce traitement. Le principe du traitement et l'importance de maintenir la position idéale de repos doivent être expliqués au patient et au personnel pour en obtenir une pleine collaboration.

Ce traitement augmente les effets souhaitables de la chimiothérapie, puisque les cavernes se ferment rapidement et les bacilles ne deviennent pas résistants. De même les formations kystiques suivant la chimiothérapie, récemment rapportées sont évitées.

Cette méthode n'offre aucun danger et peut s'appliquer à presque toutes les lésions cavitaires; elle est bien tolérée par la plupart des patients. Seule une tuberculose endobronchique, avec sténose bronchique sévère, s'oppose à ce traitement; il en est de même chez les patients porteurs de lésions cavitaires bilatérales, situées dans les segments diamétralement opposés.

L'auteur présente cinq cas typiques dont quelques-uns n'ont pas bénéficié de la chimiothérapie et la collapsothérapie dans le passé. E.O.H.

INTESTINAL MONILIASIS IN ADULTS

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INTRODUCTION

(a) *Presence of "Candida" species in stools.* Species of the genus *Candida* have been isolated from fæcal material repeatedly since Langenbeck[18] found them in the intestines at autopsy in 1839. However, it is difficult to compare and discuss these findings for various reasons. In many instances no attempt was made to identify the yeasts, while other authors merely state "yeasts seen on smear". Furthermore, the methods of isolation varied. It is obvious that the media used by bacteriologists for the routine isolation of intestinal bacteria do not provide optimal growth conditions for *Candida* species. Therefore, any estimate of the number of *Candida* species isolated from stool specimens has to be evaluated with great caution.

Le Dantec[21] found filamentous yeasts in great numbers in fæces of patients suffering from sprue, and believed sprue to be a *"véritable blastomycose intestinale"*. Castellani and Low,[9] however, thought of yeasts only as secondary invaders in cases of sprue. Ashford[2-4] constantly isolated a yeast-like fungus, *Monilia psilosis* Ashford, 1914, from the inflamed tongue and fæces of persons suffering from sprue in Puerto Rico. More than 20 years later, Langeron and Guerra[19] studied Ashford's original strains and identified them as *Candida albicans*. Ashford[3] found the same yeast in the centre of a cooked loaf of bread in an endemic area. He was able to prove that his isolated strains were pathogenic for small laboratory animals, which developed severe septicæmia with incurable mycotic ulcers. Ashford[2] found his *Monilia psilosis* (*Candida albicans*) in only 3% of persons who were apparently healthy, or at least free from gastro-intestinal disturbances. In 1917, Anderson[1] examined the stools of 175 persons; 37% of these specimens yielded yeasts on culture. Although he included pink colonies, probably non-pathogenic *Rhodotorula* species, in his counts as well as colourless strains, he concluded that yeast-like organisms were present only in relatively small numbers in stools of healthy persons. Fleisher and Wachowiak[15] found three "*Monilia*-like organisms" on examination of 92 stools of normal persons. Hannibal and Boyd[16] concluded from their observations that there is no specific relationship between yeasts and sprue. Unfortunately, the work of Nye, Zerfas and Cornwell[24] provides no reliable identification of the yeasts isolated from stools; however, it might be mentioned that they found a higher incidence of yeast-like fungi in the gastric contents from patients with achylia.

Benham and Hopkins[6] isolated 18 *C. albicans*, 13 *C. krusei* and 2 *C. parapsilosis* strains from the stools of 100 normal persons. Todd[31] examined the fæces of 1000 healthy persons, and found *C. albicans* in 9.3% of the males and 18.2% of the females. Of 314 stools, 33.1% were found by Schnoor[27] to contain *Candida* species, mostly *C. albicans*. Pasricha and Lal[25] reported a very abundant growth of "yeasts" from stools in India, but their work does not include any attempt to identify the "yeasts" and therefore becomes meaningless. *C. albicans* was isolated by Swartz and Jankelson[30] three times from 24 cases of non-specific ulcerative colitis. Lawler, Omundson and Donald[20] believe that there is no relationship between *Candida* species and intestinal parasites in the gastro-intestinal tract although the number of isolated *Candida* species reported is rather high. A high incidence of *Candida* species was also observed by Felsenfeld[14] in the fæces of "institutionalized patients". *C. albicans* was found in 19.3% of 300 new admissions and in 37.7% of 600 ward cases. Other *Candida* species (*C. parapsilosis, C. krusei*) were isolated in much smaller percentage. A correspondingly high incidence of *C. albicans* was encountered by Marples and Di Menna[22] in New Zealand. They found that 30.8% of the stools of children investigated harboured *C. albicans*.

In 1955, the Department of Bacteriology and Immunology, McGill University, Montreal, received 517 and 505 clinical specimens of stool from adults and children respectively, for bacteriological examination. The following *Candida* species were isolated, using the routine media for the isolation of the intestinal bacterial flora:

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	Adults	*Children*
C. albicans	13	23
C. krusei	3	2
C. pelliculosa	1	
C. parapsilosis		4
C. guilliermondii		4
C. scottii		1
Unidentified		1
	17	35

As has been previously mentioned, the routine media used for the isolation of intestinal bacterial flora from fæces do not provide optimal growth conditions for *Candida* species. Therefore, we decided to investigate the incidence of *Candida* species in stools of apparently healthy persons with no gastro-intestinal complaints. We used Sabouraud's glucose agar containing antibiotics (penicillin, streptomycin, actidione) the exact composition of which will be given later. Stool specimens were received from 126 males (mostly McGill students) and 152 females (mostly nurses of the Royal Victoria Hospital and McGill students). The mycological examination of these stool specimens gave the following results:

	Male	*Female*
Very heavy growth of *C. albicans*	8	11
Heavy growth of *C. albicans*	12	23
Moderate growth of *C. albicans*	5	7
Light growth of *C. albicans*	4	14
Very heavy growth of *C. krusei*	1	
No growth of yeast-like fungi	96	97
Totals	126	152

(b) *Increased occurrence of "Candida" species in stools of persons after treatment with antibiotics.* One of the side-effects of antibiotics, especially the so-called broad-spectrum antibiotics, is the sudden massive appearance of *Candida* species inside the body and on its surface.[13, 33] While *Candida* species might have been present before, without causing any clinical symptoms or any discomfort, they suddenly appear to have become more pathogenic. The same holds true for cows treated for bacterial mastitis with antibiotics.[7] Harris[17] gave a good clinical description of such signs and symptoms in the intestinal tract, and Weyler[32] described the additional skin irritation around the anus due to aureomycin. Acute prostatitis or proctocolitis was noticed one to three weeks after the use of aureomycin or terramycin was discontinued.[26] Brown[8] found an increased number of *C. albicans* colonies in stools after aureomycin therapy. The same observation was made by McGovern *et al.*,[23] who found that the average amount of *C. albicans* increased from three to eight days after treatment. Chewning[10] described colitis following the oral administration of aureomycin and terramycin, and Smith[29] concluded that the disturbance of the normal bacterial œcology by the administration of antibiotics was responsible for the development of such hitherto unestablished new clinical syndromes. An impressive report of the effect of aureomycin on the appearance of "yeasts", unfortunately not identified, came from the Mayo Clinic. Dearing and Heilman[12] examined the bacterial flora of the intestinal tract of people given aureomycin for preoperative preparation. Sixty-six patients received 750 mg. aureomycin, q.i.d. orally, and "yeasts" appeared in the stools of 36. When the dosage was reduced to 500 mg., only 2 of 11 stools yielded growth of "yeasts". With a further reduction to 250 mg. the growth of "yeasts" was not induced in any of the specimens examined. The same held true for Sulfathalidine preoperative treatment. With Sulfasuxidine preparation only 2 of 32 stools contained "yeasts". When 750 mg. aureomycin q.i.d. and 500 mg. dihydrostreptomycin q.i.d. were given, 14 of 18 specimens grew "yeasts", and a dosage of 500 mg. dihydrostreptomycin q.i.d. brought about growth of "yeasts" in 1 of 9 specimens. Sharp[28] investigated the growth of *C. albicans* during and after terramycin and sulfadiazine therapy in patients with pneumonia. In the terramycin group (a five-days' course of an average dosage of 14.2 g.) the proportion of rectal swabs from which *C. albicans* was grown rose from nil to 59%. While there was no increase in incidence of *C. albicans* during treatment in the sulfadiazine group, the proportion of rectal swabs which grew *C. albicans* rose from 5 to 20% 2-4 days after discontinuing treatment.

Investigation of Cases of Intestinal Moniliasis in Adults

Since the significance of massive occurrence of *Candida* species in stools has not yet been fully investigated, we have felt that further studies of intestinal moniliasis among adults might bring to light more information about this currently ill-defined condition. Therefore, over the past three years we have studied cases of gastro-intestinal disturbance in which no cause for the symptomatology could be found and in which stool cultures have yielded heavy growths of *Candida* species.

(a) *Bacteriological and mycological methods.* Bacteriological examination of the stool specimens included the search for *Salmonella* and *Shigella* species, *Staphylococcus pyogenes*, and pathogenic *Escherichia coli* species. For this purpose, the following media were used: tetrathionate broth, SS agar "Difco", MacConkey agar "Difco", blood agar and Chapman medium.

To examine for the presence of *Candida* species, stools were streaked on three 22 x 175 mm. slopes. Two of these contained Sabouraud's glucose agar "Difco" in which 20 units/ml. penicillin and 40 units/ml. streptomycin were included, and the third contained the same medium with 0.5 mg./ml. actidione.

(b) *Case histories.*—We have encountered 50 cases in which *C. albicans* was found to be the causative organism of gastro-intestinal disturbances. For technical reasons only seven representative cases will be reported here.

Mrs. E.B., aged 34. This patient had been treated for a pneumonia with injections of penicillin in 1948. Some time after this, she complained that she was suffering from gas and flatus, recurring mild crampy abdominal pains, loose stools, and abdominal distension, but no pruritus ani or vulvæ. She was found to have amœbiasis in 1953 and was treated with emetine, carbarsone, diodoquin, and chloroquine in 1953 and 1954. Regular sigmoidoscopic examinations since then have revealed no evidence of amœbiasis.

Investigation of her gastro-intestinal tract, including barium enema, barium meal, and sigmoidoscopy, done in November 1954, did not reveal any organic abnormality. No amœbæ were found. However, the stool cultures showed, besides a light growth of *E. coli*, a heavy growth of *C. albicans.*

The patient was given a course of gentian violet, 30 mg. t.i.d., for three weeks. This treatment resulted in an almost complete relief of her signs and symptoms. Stool cultures done after this treatment yielded no *C. albicans*, but a moderate growth of *E. coli* and light growth of *Proteus mirabilis.*

In March 1955, the same signs and symptoms recurred and a stool culture disclosed a very heavy growth of *C. albicans*, and *E. coli.* No evidence of amœbiasis was found on sigmoidoscopy. The patient was given nystatin (Mycostatin), one tablet t.i.d., for one week, and gentian violet, 30 mg. t.i.d. for three weeks, which gave excellent results clinically. A follow-up culture showed only a very light growth of *C. albicans* and a heavy growth of *E. coli.* The patient was free from gastro-intestinal complaints.

Bleeding from rectal mucosa and passing mucus, but not diarrhœa, recurred at the end of June 1956. A stool culture done on July 10, 1956, produced again a very heavy growth of *C. albicans.*

Mr. B.H.W., aged 35. This patient had been given broad-spectrum antibiotics for an occasional "cold". Early in 1955, he developed marked pruritus ani and an extensive seborrhœic dermatitis in the perineum as well as in the axillæ and on the feet, but moniliasis was not recognized. He also suffered from much gas, flatus and soreness in the abdomen, as well as occasional loose stools. During the whole year 1955 he had constant pains in the rectum with occasional spontaneous bleeding at defæcation. Sigmoidoscopic examination showed only a friable mucous membrane; no ulceration could be detected. Barium examinations did not disclose any organic abnormality. Various treatments were tried without much success.

In September 1955, he was given erythromycin and neomycin for scattered boils. The dermatitis of the groins, perineum and axillæ became worse after this treatment.

In December 1955, scrapings from the groins, perianal region and feet revealed the presence of yeast-like fungi, and cultures yielded a very heavy growth of *C. albicans.*

In February 1956, the stool cultures showed a very heavy growth of *C. albicans.* No bacteria were grown from this specimen.

The intestinal moniliasis was treated with Mycostatin, one tablet t.i.d. for a week, to be followed by gentian violet, 30 mg. t.i.d. for three weeks.

The relief of his rectal pains, gas, flatus, and abdominal pains was dramatic—within three days after starting on Mycostatin. Furthermore, corresponding to this relief of gastro-intestinal complaints, a stool specimen cultured a week after the beginning of treatment revealed the complete absence of *C. albicans* as well as a light growth of a *Paracolobactrum* species and *Staphylococcus pyogenes.* Two weeks after this treatment had been started, the patient, who lives in Quebec City, stated in a letter: "The one thing which has improved tremendously is the internal burning and itching when I have a bowel movement. Since I started the internal medication I have had practically no burning or itching. I have no diarrhœa any longer. It is really wonderful to be able to defæcate almost like a normal person".

Skin scrapings from the various sites involved continued to yield cultures of *C. albicans.*

On March 27, 1956, a stool specimen showed a very light growth of *C. albicans* and a heavy growth of *E. coli.*

The patient then reduced the dosage to two gentian violet pills (30 mg.) instead of the three he had been taking before. Thereafter, the stool culture yielded a heavy growth of *C. albicans* besides a moderate growth of *E. coli* and *S. pyogenes* (April 8, 1956). The patient was advised to return to the original dosage. A very light growth of *C. albicans*, a moderate growth of *Aerobacter aerogenes* and a heavy growth of *Streptococcus fæcalis* were found in a stool specimen on May 2, 1956. The patient continued to take 30 mg. gentian violet t.i.d., and was practically free of all previous gastro-intestinal complaints while on this treatment.

Mrs. E.P. aged 40. In January 1955, the patient was suffering from pneumonia and was given Achromycin (tetracycline) for ten days. She developed loose stools and a burning feeling in the rectum immediately. The patient had one or two loose stools in the morning, and another one or two at later times daily. Furthermore, she passed mucus and some liquid bowel contents.

The persistent signs and symptoms induced the patient to come for examination early in May 1955. Barium meal, barium enema, and sigmoidoscopic examinations failed to demonstrate any organic abnormality. Stool examinations for amœbæ were all negative. A stool culture on May 6, 1955, revealed a very heavy growth of *C. albicans* and a moderate growth of *E. coli.* It was felt that the fungus might be the cause of her disturbances.

On May 16, 1955, treatment with gentian violet was started. The patient received 30 mg. gentian violet, t.i.d. for one week, and b.i.d. for the following week. The dosage was reduced to 30 mg. daily the third week. On June 20, 1955, the patient felt much better and the stools became formed after this date. A stool specimen cultured at this time showed only a light growth of *C. albicans* besides a moderate growth of *E. coli.* The patient was then given Mycostatin (nystatin), one tablet t.i.d. for four days, followed by a ten-days' course of gentian violet, 30 mg. t.i.d. Thereafter, this treatment was repeated. On August 3, 1955, the stool cultures revealed only a rare colony of

C. albicans in three large tubes, and a moderate growth of *E. coli*. The patient felt well and when seen on September 15, 1955, all previous gastro-intestinal signs and symptoms had disappeared or decreased.

Mr. G.B., aged 44. In June 1953, he complained of loose stools and abdominal discomfort, which he had noticed off and on for the previous four months. At this time, a barium enema and a barium meal, with small bowel follow-through, did not show any organic abnormality. Sigmoidoscopic examination showed no lesion of the mucous membrane, but swabs revealed the presence of *Entamœbæ bütschlerii*. He was given a course of terramycin, 250 mg. q.i.d. for one week. After this treatment he developed burning sensations in the rectum and persistent pruritus ani, and the loose stools continued. Some hæmorrhoids appeared and were injected. However, the pruritus persisted. An anticholinergic drug did not improve the loose stools or discomfort.

In December 1953, a stool culture revealed a heavy growth of *C. albicans*. The patient was given gentian violet, 30 mg. t.i.d. for ten days. This treatment was repeated after a three weeks' interval. At the end of February 1954 he felt much better. The diarrhœa, abdominal discomfort, and the pruritus ani had stopped. A stool culture at this time, and again in April 1954, showed no yeast-like fungi to be present. Bacteriological examinations of these stool specimens indicated moderate and heavy growth of *E. coli* respectively.

He had no recurrence of the previous signs and symptoms, and another stool culture in February 1956 showed only a very light growth of *C. albicans* besides a moderate growth of *E. coli*.

Mrs. M.S., aged 50. This patient was first seen in December 1952. She had been suffering from constant diarrhœa—never more than five stools daily—during the previous year. Other complaints were of much gas, flatus, abdominal distension, abdominal pains, and a very distressing burning in the rectum. No antibiotics had ever been taken by this patient.

X-ray examination revealed a functioning gall-bladder containing many radio-opaque stones. A barium meal and sigmoidoscopy did not reveal any organic abnormality. A gastric analysis showed the presence of free hydrochloric acid. A barium enema disclosed a minimal diverticulosis of the sigmoid colon. Repeated stool examinations gave no evidence of amœbiasis. Stool cultures yielded a heavy growth of *C. albicans* besides a normal intestinal flora.

A low roughage diet and antispasmodic drugs were prescribed. This treatment resulted in some relief of the diarrhœa, but all other symptoms remained unchanged. Furthermore, the patient now complained of pruritus ani and increasing fatigue.

In November 1953, the stool specimens still gave growth of numerous colonies of *C. albicans*. A ten days' course of Entero-vioform, one tablet t.i.d., did not relieve any of her symptoms.

In February 1954, a stool culture again revealed a heavy growth of *C. albicans*. Gentian violet, 30 mg. t.i.d. for one week, was prescribed and the same treatment was repeated three weeks later. Whereas the first course of gentian violet did not reduce the growth of *C. albicans* from a stool specimen, the second almost eliminated the yeast-like fungus from the stool, as well as suppressing the formation of gas and flatus. The diarrhœa had stopped, but the other symptoms persisted.

Another course of gentian violet treatment was then tried. However, the results were not satisfactory and a stool specimen in May 1954 showed a heavy growth of *C. albicans* and the normal flora of bacteria.

The dosage of gentian violet was now raised and 60 mg. t.i.d. was given for three weeks. There was no relief of any of the symptoms and the drug caused more diarrhœa. Stool cultures done during and after this course of treatment continued to demonstrate a very heavy growth of *C. albicans* and a moderate growth of *Proteus mirabilis* and *Paracolobactrum intermedium*.

During the summer of 1954 the patient tried yoghurt milk without any benefit. The stool cultures, too, remained unchanged.

In September 1954, Hibitane (1:6-di-4-chlorophenyldiguanido-hexane) was given for a number of weeks. The dose was increased gradually from 100 mg. t.i.d. to 600 mg. t.i.d. Although the diarrhœa and the pruritus ani diminished, the stool cultures, done once a month, always showed a very heavy growth of *C. albicans* and a light growth of *E. coli*.

A cholecystectomy was done in January 1955. Recovery was uneventful.

In February 1955, Mycostatin, one tablet t.i.d., was given for eight days. All her signs and symptoms disappeared or decreased. Four days after termination of this treatment a stool specimen grew only *E. coli*; no yeast-like fungi were found in the cultures.

Within several weeks, however, all her signs and symptoms returned and stool cultures again produced a heavy growth of *C. albicans*.

The condition persisted until January 1956, when she reported again. The patient admitted that she had practically no more flatulence or pruritus ani, but still had diarrhœa with urgency of going to stool. Gas and belching were her outstanding complaints. Stool cultures again showed a heavy growth of *C. albicans* besides a light growth of *E. coli*.

This time she was given lozenges containing 5 mg. of cetyldimethylbenzylammonium chloride to suck 8-10 times daily. No change occurred either in the patient's condition or in the stool cultures (a very heavy growth of *C. albicans* and a light growth of *E. coli*) at the conclusion of the treatment. Since quaternary ammonium compounds are destroyed in an alkaline medium, such as is found in the gastro-intestinal tract, no improvement could have been expected.

Mrs. F.T., aged 70. In June 1953, the patient complained of fatigue, excessive gas and belching, abdominal distension, lower abdominal pains, and pruritus ani from which she had been suffering for several months. She also complained of chronic constipation for many years; she never had diarrhœa and had never taken any antibiotics.

The gall-bladder was found to be normal on x-ray examination. Barium enema showed a moderate spasticity of the left half of the colon. Barium meal with small bowel follow-through and sigmoidoscopy did not demonstrate any organic abnormality. A gastric analysis, done later, indicated normal amounts of free hydrochloric acid. Repeated stool examinations revealed no evidence of amœbiasis; however, the stool cultures demonstrated a very heavy growth of *C. albicans*.

Sodium iodide, 600 mg. t.i.d.p.c., was given, but because of symptoms of iodism the treatment had to be stopped.

In August 1953, her barium studies were repeated and again did not reveal any pathological features. The moniliasis persisted. Another physician prescribed aureomycin, vitamin B complex injections and daily taking of yoghurt milk. This treatment did not influence her condition.

In November 1953, the patient was given a two weeks' course of gentian violet, 30 mg. t.i.d., which did not alleviate her condition nor did it change the number of *C. albicans* colonies cultured from the stool specimens.

In January 1954, the patient took Entero-vioform for one week and then gentian violet, 60 mg. t.i.d., for two weeks. Her gas, belching and distension, fatigue and pruritus ani became much relieved, and only a light growth of *C. albicans* was obtained on culture of a stool specimen at that time. However, a month later, a stool culture showed a heavier growth of *C. albicans* and her complaints had again become more pronounced.

From March to September 1954 the patient received a number of courses of gentian violet, 30 mg. t.i.d. for

two weeks at a time. The treatment seemed to reduce the formation of gas and distension, but the other signs and symptoms always recurred. Monthly stool cultures revealed a very heavy growth of *C. albicans* and a light to moderate growth of *E. coli* and *S. fæcalis.*

In September 1954 Hibitane (1:6-di-4-chlorophenyl-diguanido-hexane) was given. The dose was gradually increased from 100 mg. t.i.d. to 1000 mg. t.i.d. The drug produced neither ill effects nor any improvement of the condition. Stool cultures remained unchanged as well.

In October 1954, she was given gentian violet, 60 mg. t.i.d., for two weeks and then Mycostatin, one tablet t.i.d., for two weeks. While she stayed on this latter preparation the stool cultures yielded only a light growth of *E. coli* and no yeast-like fungi. All her signs and symptoms diminished or disappeared, only to recur as soon as the medication was stopped.

Stool cultures done in December 1954 and January 1955 revealed a very heavy growth of *C. albicans* and a heavy growth of *E. coli* and light growth of *S. fæcalis.*

Mycostatin, one tablet t.i.d., was again given for eight days in February 1955. The stool culture became negative for *C. albicans;* there was only a light growth of *E. coli* and *S. fæcalis.* Her condition was very much improved.

The signs and symptoms accompanied by a heavy growth of *C. albicans,* light growth of *E. coli* and light growth of *P. mirabilis* recurred in March 1955. A six weeks' course of treatment with Mycostatin, one tablet t.i.d., improved her condition considerably. *C. albicans* had disappeared from the stool cultures and there remained only a heavy growth of *E. coli.*

In June and September 1955 stool cultures revealed a moderate growth of *C. albicans, E. coli* and *P. mirabilis* and the patient continued to feel much better.

In November and December 1955 treatment with Mycostatin, one tablet t.i.d., was continued for three weeks. The patient felt much better while on this course of medication. The improvement lasted for several weeks after the conclusion of this treatment.

A stool culture on January 22, 1956, demonstrated again a heavier growth of *C. albicans* besides a heavy growth of *E. coli.* At the end of January 1956, the patient was complaining again of gas and abdominal distension, pruritus ani, and actual burning with some excoriation around the anus. Cultures from swabs taken from a sore tongue revealed the presence of *C. albicans.* An examination of the stool in March 1956 disclosed a very heavy growth of *C. albicans* and a heavy growth of *E. coli.* Her signs and symptoms remained unchanged.

Mrs. F.W., aged 73. This patient was admitted to the Roval Victoria Hospital in the beginning of November 1953. She was suffering from diabetes and diabetic neuropathy as well as a chronic cystitis. There were no gastro-intestinal complaints at the time of her admittance.

Her diabetes was controlled with diet and insulin. After investigation, the urinary tract infection was treated with terramycin, 250 mg. q.i.d. By the eighth day of treatment with terramycin she had developed a severe diarrhœa, and also complained of crampy pains, weakness and loss of appetite. Stool cultures showed a very heavy growth of *C. albicans.* No other pathogenic micro-organisms were cultured.

Gentian violet. 60 mg. t.i.d., was given over a period of one week. The same treatment was repeated two weeks later.

No growth of veast-like fungi was obtained on culture ten days after the gentian violet treatment had been discontinued.

There have been no more bouts of diarrhœa or gastro-intestinal complaints during the following two years. Several stool cultures were done in February 1956. They showed a light growth of *Pseudomonas æruginosa* while the yeast-like fungi had completely disappeared.

DISCUSSION

(a) *Diagnosis and symptomatology of intestinal moniliasis.* The *Candida* species are fungi of a low and varying degree of pathogenicity. Therefore it is hard to evaluate the meaning of the presence of *Candida* species in stools, even if they are present in large numbers.

Intestinal moniliasis in adults is characterized by some or all of the following signs and symptoms: (1) Recurrent diarrhœa or even constant loose stools, generally not more than 4-5; after some months stools might become soft, 1-2 daily: (2) excessive gas, flatus, and abdominal distension; (3) abdominal pains, often crampy; (4) pains in the rectum, sometimes burning in character; (5) pruritus ani; (6) occasional bleeding from rectal mucosa, at defæcation or even entirely spontaneously.

The establishment of such a diagnosis requires the ruling out of all other possible causes by means of barium studies, sigmoidoscopy, and bacteriological and parasitological investigative methods. If these examinations prove negative and a significant growth of *Candida* species is obtained from stool or sigmoidoscopic swabs on a suitable medium, a diagnosis of intestinal moniliasis should be considered.

In our series, these requirements were met. Furthermore, when treatment resulted in relief or disappearance of symptoms and signs, there was a corresponding reduction or absence of *Candida* species in the stool cultures. On the other hand, the recurrence of signs and symptoms was always associated with the reappearance or heavier growth of the *Candida* species in the specimens.

We have never observed a spontaneous disappearance of *C. albicans* from stool specimens.

In each of our cases a complete bacteriological investigation of the intestinal flora was done and revealed the presence of the usual intestinal bacteria.

We are fully aware that there are cases in which a heavy growth of *Candida* species from stool specimens is observed and the patients have none of the previously described signs and symptoms. In fact, we have observed and followed such cases during the last three years. A parallel might here be drawn between such cases and the frequent presence of *C. albicans* in the oral cavity without causing the signs of thrush. The same holds true for the bacterial

flora of the nasopharynx (pneumococci and streptococci).

(b) *Treatment.* In our experience, neither sodium iodide, Vioform, Hibitane nor cetyldimethylbenzylammonium chloride produce any beneficial results.

Nystatin (Mycostatin) treatment resulted in dramatic reduction or disappearance of *C. albicans* from stools on culture, generally accompanied by clinical improvement. However, as soon as the Mycostatin treatment was discontinued there was either a much increased growth or a reappearance of *C. albicans* in the stool cultures together with the return of the clinical signs and symptoms. One explanation of this phenomenon may be the fact that *C. albicans* can invade and parasitize the intestinal wall, as shown by Beemer, Pryce and Riddell.[5] Mycostatin, because of its physico-chemical properties,[11] would be unable to get into close contact with the fungus there and thus completely eradicate the causative organism in the gut.

Administration of Mycostatin, however, proved to be the most valuable procedure in corroborating the diagnosis and establishing the symptomatology of intestinal moniliasis.

So far, gentian violet seems to be the most useful therapeutic agent although clinical cure was secured in only a few cases. Cases of short duration seem to be more amenable to treatment than those of long standing.

SUMMARY

The literature on the presence and on the increased occurrence of *Candida* species in cultures of stool specimens after treatment with antibiotics is reviewed. A survey revealed the incidence of *Candida* species in stools of young adults (males 23.8%, females 36.2%).

Seven case histories representative of 50 cases of intestinal moniliasis diagnosed and followed during the last three years are reported. The study of this series of cases of intestinal moniliasis allowed us to elicit the necessary diagnostic procedure and to establish the symptomatology of intestinal moniliasis. Intestinal moniliasis was found to be characterized by a heavy growth of *Candida* species, especially *C. albicans*, on stool culturing, and the presence of all or some of the following signs and symptoms: loose stools or diarrhœa, bleeding from the rectal mucosa, flatulence, formation of gas, distension, abdominal pains, pain in the rectum, and pruritus ani.

In a few cases only, treatment with gentian violet produced an apparent cure. Treatment with Mycostatin resulted in only a temporary improvement of the condition corresponding to the temporary disappearance or the reduced growth of *Candida* species from the stool cultures.

Intestinal moniliasis has been shown to be a well-defined clinical entity which occurs more frequently in adults than is generally accepted. This condition is demanding more attention. It can easily be diagnosed by the procedure—including the use of Mycostatin (nystatin)—followed in our series.

The authors are indebted to Drs. C. Miller Ballem and R. D. McKenna for permission to include their cases in this series.

REFERENCES

1. ANDERSON, H. W.: *J. Infect. Dis.*, 21: 341, 1917.
2. ASHFORD, B. K.: *J. A. M. A.*, 64: 1893, 1915.
3. *Idem*: *Am. J. M. Sc.*, 150: 680, 1915.
4. *Idem*: *J. A. M. A.*, 93: 762, 1929.
5. BEEMER, A. M., PRYCE, D. M. AND RIDDELL, R. W.: *J. Path. & Bact.*, 68: 359, 1954.
6. BENHAM, R. W. AND HOPKINS, A. MCH.: *Arch. Dermat. & Syph.*, 28: 532, 1933.
7. BLANK, F.: Unpublished data.
8. BROWN, F.: *Antibiotics & Chemother.*, 2: 5, 1952.
9. CASTELLANI, A. AND LOW, G. C.: *J. Trop. Med. Hyg., Lond.*: 16: 33, 1913.
10. CHEWNING, C. C., JR.: *Virginia M. Month.*, 79: 136, 1952.
11. COUNCIL ON PHARMACY AND CHEMISTRY: *J. A. M. A.*, 160: 776, 1956.
12. DEARING, W. H. AND HEILMAN, F. R.: *Proc. Staff Meet. Mayo Clin.*, 25: 87, 1950.
13. Editorial: *Brit. M. J.*, 1: 1184, 1950.
14. FELSENFELD, O.: *Am. J. M. Sc.*, 207: 60, 1944.
15. FLEISHER, M. S. AND WACHOWIAK, M.: *Ibid.*, 168: 371, 1924.
16. HANNIBAL, E. A. AND BOYD, M. F.: *Am. J. Trop. Med.*, 1: 165, 1921.
17. HARRIS, H. J.: *J. A. M. A.*, 142: 161, 1950.
18. LANGENBECK, B.: *Froriep's Neue Notizen*, 12: 145, 1842.
19. LANCERON, M. AND GUERRA, P.: *Ann. de parasitol*, 16: 36, 1938.
20. LAWLER, F. C., OMUNDSON, D. V. AND DONALD, E. W.: *Am. J. Pharm.*, 114: 47, 1942.
21. LE DANTEC, A.: *Compt. rend. Soc. de biol., Par.*, 64: 1066, 1908.
22. MARPLES, M. J. AND DI MENNA, M. E.: *J. Path & Bact.*, 64: 497, 1952.
23. MCGOVERN, J. J. *et al.*: *New England J. Med.*, 248: 397, 1953.
24. NYE, R. N., ZERFAS, L. G. AND CORNWELL, M. A.: *Am. J. M. Sc.*, 175: 153, 1928.
25. PASRICHA, C. L. AND LAL, S.: *Indian M. Gaz.*, 74: 682, 1939.
26. Queries and Minor Notes: *J. A. M. A.*, 146: 767, 1951.
27. SCHNOOR, T. G.: *Am. J. Trop. Med.*, 19: 163, 1939.
28. SHARP, J. L.: *Lancet*, 1: 390, 1954.
29. SMITH, D. T.: *Ann. Int. Med.*, 37: 1135, 1952.
30. SWARTZ, J. H. AND JANKELSON, I. R.: *Am. J. Digest. Dis.*, 8: 211, 1941.
31. TODD, R. L.: *Am. J. Hyg.*, 25: 212, 1937.
32. WEYLER, H. L. C.: *Rhode Island M. J.*, 33: 137, 1950.
33. WOODS, J. W., MANNING, I. H., JR. AND PATTERSON, C. N.: *J. A. M. A.*, 145: 207, 1951.

RÉSUMÉ

Cet article débute par une revue des auteurs ayant contribué à l'étude de l'espèce *Candida* dans la culture des selles après administration d'antibiotiques. On a relevé la présence de ce micro-organisme dans les selles de jeunes adultes (23.8% chez les hommes, 36.2% chez les femmes). Les faits cliniques de sept malades sont présentés, extraits d'une série de 50 cas diagnostiqués dans les trois dernières années. Cette série a permis aux auteurs de cet article d'établir la symptomatologie de cette affection ainsi les procédés diagnostiques nécessaires à son dépistage. Ceux-ci consistent en une croissance abondante de *Candida*, particulièrement du *C. albicans* dans les selles. Les symptômes comprennent de la diarrhée, une muqueuse rectale hémorragique, de la flatulence, du ballonnement, des douleurs abdominales et rectales et du prurit anal.

Le violet de gentiane n'apporta une guérison apparente que dans quelques cas. La MYCOSTATINE (nystatine) ne donna qu'une amélioration passagère se traduisant par une diminution ou une suppression temporaires du *Candida* dans les selles. La moniliase intestinale est une entité clinique bien établie qui se retrouve chez l'adulte et requiert plus de soins qu'on ne lui en a apporté jusqu'à présent. On peut arriver au diagnostic par les moyens indiqués ci-haut, y compris l'emploi de la nystatine.

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Case Reports

REPORT OF A CASE OF THROMBOSIS OF THE ABDOMINAL AORTA WITH INVOLVEMENT OF THE LEFT RENAL ARTERY

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INCREASING INTEREST in diseases of the abdominal aorta, and in the effects of unilateral kidney disease in the pathogenesis of hypertension, has prompted us to report this unusual case.

The patient, D.M.B., was admitted to Christie Street Hospital, Toronto, in 1941, complaining of weakness and pain in the lower limbs. His history dated back to 1939, when, at the age of 43, he experienced tiredness and weakness in his thighs and legs with exertion. Before 1939 he could play 36 holes of golf without difficulty; within the next few years he progressively reduced the number of holes to 9; and by 1941 could not play at all because of weakness in the legs.

Two years after the onset of weakness, and three months before admission to hospital, he developed a burning pain and stiffness in his anterior thigh and calf muscles with exertion. Rest relieved the pain within minutes. If the exertion was continued, the pain would spread to the buttocks and back.

One month before entering hospital he found it difficult to hold a book or telephone for any length of time because of weakness in the arms. Because of increasing pain and lack of improvement with rest, admission to hospital was advised by his physician.

He was well developed and well nourished. Examination of his heart revealed an inconstant systolic apical murmur, regular rhythm, rate 75; blood pressure 127/92-85 mm. Hg. An ECG was interpreted as normal. There were no abnormalities in his abdomen. The findings on neurological examination were normal except for slight asymmetry of the face, weakness of the voice after conversation, and marked symmetrical weakness of all muscles of the arms and legs. No atrophy, fibrillation or spasticity was observed, and all stretch reflexes were normal. There were no signs of pyramidal tract disease, and no abnormalities in superficial or deep sensory appreciation. Laboratory tests included the following: Routine laboratory tests were all normal. Because he handled lead pipes his urine was examined for lead; the content was 0.9 mg. per litre; the non-protein nitrogen (NPN) was 27 mg. %. After intravenous injection of phenolsulfonphthalein (PSP) 70% of the dye was excreted in the urine in two hours. Cerebrospinal fluid was normal.

Two diagnoses were considered as a possible cause of his disabilities: (1) *myasthenia gravis*, (2) *polyneuritis, cause unknown.*

He was treated with prostigmine bromide 15 mg. up to nine times a day. There was subjective improvement but it was slow and during 2½ years in hospital he was able to walk only with the help of canes. He was still walking with assistance in 1945. Marked weakness of the legs persisted, especially of the left. Power in his arms was still diminished. He remained at home doing limited household chores.

In 1946, suddenly his right arm and leg became weak and his head and face felt heavy. There was gradual improvement over the next three weeks, but there was some measure of weakness which did not disappear for several months.

He was admitted to Sunnybrook Hospital in 1948 because of severe low back pain which came on while he was sitting down in a chair; instead of settling into the chair he fell to his knees. The next day he felt stiff and was unable to roll over on his side. Examination revealed weakness of all limbs. His face looked loose and flabby. (This he stated subsequently was his usual appearance.) There was diminished muscle power and fatigue in all muscles with movement, and any attempt to use the muscles induced fatigue and increased weakness. There was some tenderness over sacroiliac areas. His blood pressure was 130/80 mm. Hg, and the specific gravity of the urine was 1.029. After repeated examinations and consultations he was considered to be suffering from anxiety state or hysteria.

From 1949 on he began to improve subjectively so that he could walk some 200-300 yards at a slow pace without canes. He would still experience hip and leg weakness and pain, relieved by rest.

In 1952 he began to experience daily headaches. These came on some five to ten minutes after rising and were characterized by a sensation of pressure or throbbing at the back and top of the head, lasting some two to four hours. No drug relieved him. About the same time he began to have nocturia some three times, $\frac{(D}{(N} = \frac{6\text{-}8)}{3)}$

His family noticed visible pulsations over his temporal regions. He consulted a physician, who found that he had hypertension (220/110).

On low salt diet and sedatives the patient did not improve over the next six months. He was then referred to a urologist (Dr. C. M. Spooner), who in the course of investigation found that the left kidney did not excrete Diodrast. At cystoscopic examination the left ureter could not be catheterized. In January 1953 a translumbar aortogram (Fig. 1) showed a *block in the aorta up to and including the left renal artery.* Extensive collateral circulation was present.

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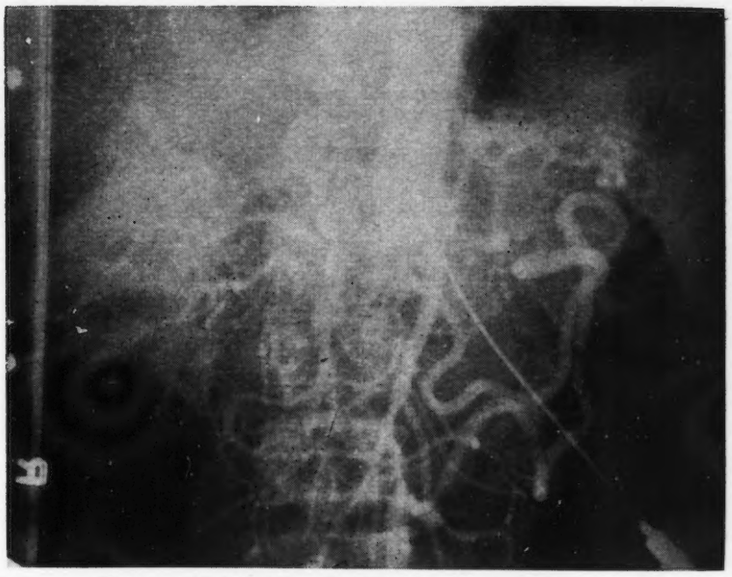

Fig. 1.—Translumbar aortogram taken in January 1953.

With the diagnosis established, it was reasonably easy in the course of an examination in March 1953 to ask pertinent questions and look for specific signs. His symptoms of pain in calf, thigh and hip were still present on walking five to ten blocks, or climbing one flight of stairs. Rest invariably relieved the pains. He also admitted that his feet and legs were cooler than usual, especially in cold weather. From 1939 he had a decrease in libido, and as well a variable degree of impotence. Further questioning revealed that his thigh and leg muscles, which were always well developed, had lost about a third of their size in the past ten years. His daily headaches were just as bad as ever. He still had nocturia up to three times. He also had experienced periodic epigastric pain, typical of peptic ulcer. A radiograph in 1948 at Toronto Western Hospital showed a duodenal ulcer. He followed his diet and drugs only when symptoms occurred.

His wife felt her husband's disposition had definitely deteriorated over the years in that he was more irritable, subject to depressed feelings, and more difficult to live with.

Examination in March 1953 revealed a well-developed and nourished plethoric-looking male, who was mentally alert and co-operative but concerned about his health. Weight 141 lb. (loss of 3 lb. in 6 months, 24 lb. in 2 years). Height 5 ft. 9½ in. His eyelids looked puffy, but comparison with a picture taken as a young man revealed this same appearance. Scalp vessels (arteries), especially in the temporal area, were visible and palpable. Breath sounds were somewhat impaired over left chest. There was no apparent cardiac enlargement. No murmurs were audible over any part of chest. The rhythm was regular, and the aortic second sound was accentuated. Blood pressure: right arm 210/105, left arm 220/110.

On abdominal examination an aortic pulsation was observed in the epigastrium. A bruit was easily heard on auscultation in this area. A small reducible right inguinal hernia was evident. The testes were normal in size, though somewhat softer in consistency, and gave a normal response to pressure.

The 12 cranial nerves were not unusual, except that the fundi revealed arteries that were irregular and narrow, with right-angle crossing and some venous nicking.

Femoral arteries were just barely palpable, right better than left; popliteal vessels were not felt; the dorsalis pedis and posterior tibial had weak pulsations. Toes and feet were cooler than thighs.

	Rt.	*Left*	
Measurement of calves	13″	12½″	Muscle power
Measurement of thighs	16″	16″	good throughout.

Skin, nails, and fat pads were well preserved. Some hair was present on both big toes. There was, on raising the legs, no undue pallor for two minutes. On dependency, no undue rubor occurred. Venous filling time: right 12 seconds, left 15 seconds. No blood pressure was measurable in legs.

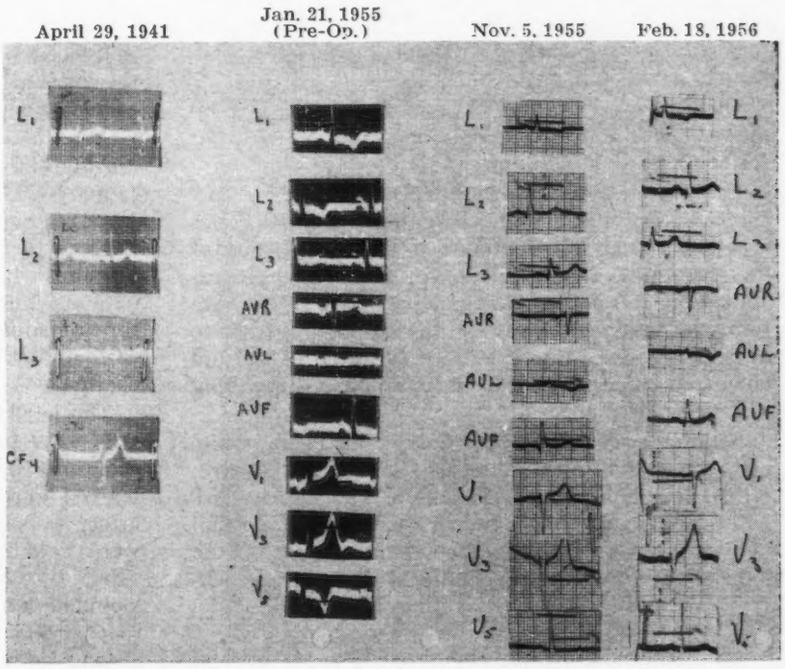

Fig. 2.—Composite picture of the electrocardiograms of this patient, indicating changes compatible with myocardial damage.

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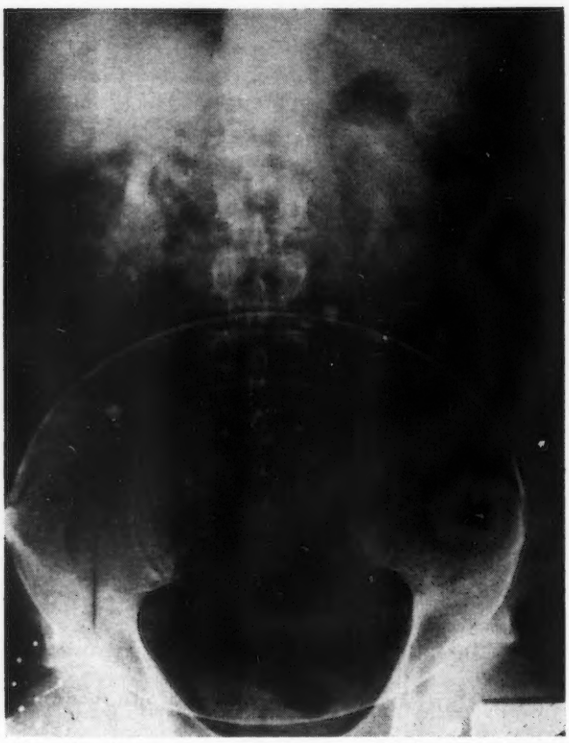

Fig. 3.—Intravenous pyelogram (Urokon) taken in December 1954.

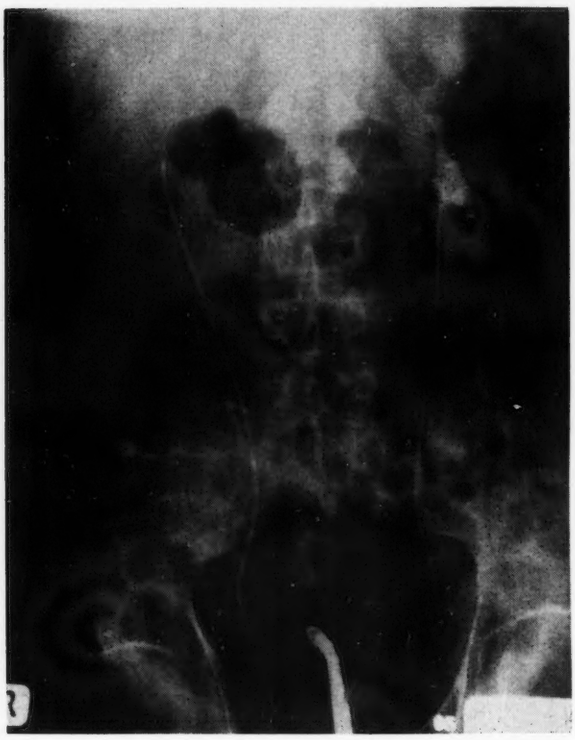

Fig. 4.—Retrograde pyelogram taken January 1955.

June 1953, Hb level 98%; white cell count 12,000 with a normal smear and differential. Sedimentation rate 15 mm. in 1 hr. (Westergren). Prothrombin time was 12 seconds, control 12 seconds. Bleeding time was 1-2 minutes; clotting time 11 minutes; platelet count 400,000. Chest film showed cardiac size normal, lungs clear. Flat plate of abdomen showed some calcific nodes.

On August 24, 1954, blood pressure in right arm was 220/120, left arm 210/100. Oscillometric readings: brachials 4 units, right thigh 1 unit, left ½ unit, calves, ankles—nil.

On December 15, 1954, he was admitted to Sunnybrook Hospital for re-evaluation, and in particular for consideration of surgery.

Laboratory examination revealed a high free gastric acid up to 86 units. A gastro-intestinal series showed a small diverticulum of the 3rd portion of the duodenum but no ulcer. On sigmoidoscopic examination a small sessile polyp was seen 23 cm. from the anus. A biopsy of this tissue proved it to be a benign lesion and it was fulgurated. A barium enema revealed several diverticula in the descending and sigmoid colon.

Sedimentation rate was 27 mm. in 1 hr.; white cell count 8800; normal smear; VDRL test negative; NPN 39 mg. %; serum cholesterol 190 mg. %; PSP 35% — 1 hr. and 10% — 2nd hr. A 2-hour Mosenthal test showed a variation in specific gravity from 1.020-1.025, and a normal ratio of day to night volume: $\frac{D}{N} = \frac{715 \text{ c.c.}}{280 \text{ c.c.}}$

An intravenous pyelogram (Fig. 3) using Urokon revealed a delay in excretion of dye from both kidneys, more especially on the left side. The left side was not seen clearly at any time. The calices and pelvis of the right kidney appeared normal, whereas the left was considerably smaller.

Cystoscopic examination: On this occasion the urologist managed to pass a catheter up the left as well as the right ureter. Excretion of urine from the right side was 50 c.c. and the left side only 4 c.c. in the same length of time. Smears of the sediment of urine revealed no pus cells from either ureter, and there was no growth of bacteria on culture.

Injection of contrast dye in the left ureter showed the left kidney to be smaller but with no deformity of either major or minor calices (Fig. 4).

After assessing the data it was believed that removal of the left kidney would prove helpful. On January 22, 1955, Dr. C. Aberhart (Chief in Urology) removed an adherent left small kidney (Fig 5). Except for a temporary cardiac irregularity in rhythm, which subsided soon after operation, the patient withstood the procedure well. His blood pressure remained unchanged throughout the operation, with no abrupt change after the renal pedicle was clamped.

The left kidney was reported by Dr. A. J. Blanchard, Director of Laboratories, as weighing 116 grams. It was pale and smooth, and had a grossly scarred surface. The largest radical of the renal artery was very small, and some of its branches were obliterated by atheroma and thrombus (Fig. 6). Microscopically the significant findings included a marked sclerosis and narrowing of the renal artery. There was a large, wedge-shaped scar at one point. Elsewhere there were large areas of scarring and fibrosis of the glomeruli (Fig. 7). The

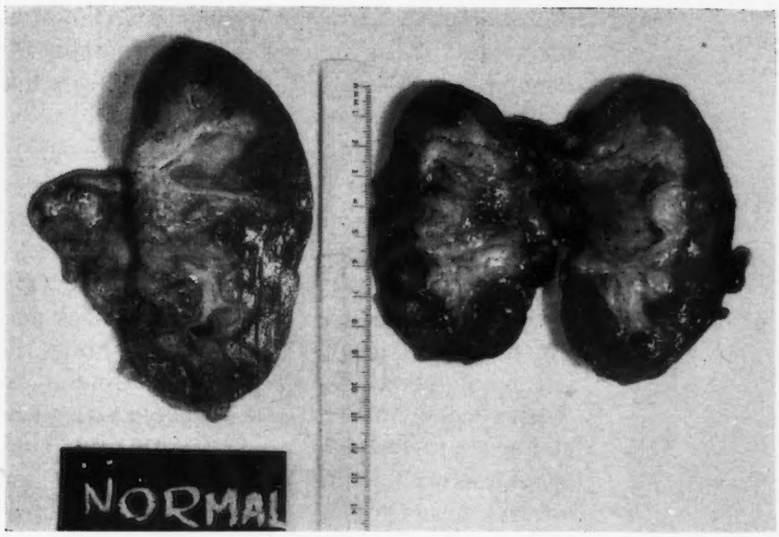

Fig. 5.—Pictured above is the removed kidney (right), much reduced in size, compared to a normal kidney (left) of a patient of similar weight and height.

other glomeruli showed marked atrophy and pericapsular fibrosis. Large collections of chronic inflammatory cells were present throughout. The arteries and arterioles were universally thickened and narrowed.

Since the operation in January 1955, this patient has been examined on several occasions and the following significant facts were noted: Headaches ceased the day after removal of the kidney. On this day he was allowed up and took a few steps. The patient's observation about freedom from headaches was spontaneous. He has not suffered a headache since. His general health has improved and he has been more alert and ambitious. His disposition has changed for the better. He took up again bowling, golfing and fishing and he resumed his hobby of painting.

Enquiry revealed he passes urine only once a night compared to two and three times before. His weight had gone up to 168 lb. (from 141). His exercise tolerance was still limited to ½ mile due to weakness followed by pain in his thighs and calves. His libido and impotence did not change.

On repeated examinations there was a gradual fall of blood pressure, 170/80 mm. Hg on July 28, 1955, to 140/75 on November 12, 1955, and 140/75 in February 1956. The aortic second sound was no longer accentuated. One could not see pulsations in the temporal vessels. His blood and urine examinations were still negative. PSP 16% in 15 minutes, 18% in 1 hr. 10 minutes, 12% in 2 hr. 10 minutes—total 46%. NPN has also been normal. Sigmoidoscopic examination up to 25 cm. revealed no abnormalities.

His most recent examination was on Jan. 19, 1957. He had had a transient cerebral vascular episode with improvement. B.P. was 130/75 (Fig. 8).

DISCUSSION

Although R. Graham in Great Britain has been credited with the first description in 1814 of thrombosis of the abdominal aorta, it was not until 1923 that Leriche rediscovered this lesion. By 1940 he had put the entity on a clinical basis, and for this reason it has been called the "Leriche syndrome".[1] This syndrome has been described as intermittent claudication of calves, thighs and hip areas, with impaired or absent pulsations from the femorals down, as well as loss of libido, with which there may be impotence.

In recent years a greater number of cases have been diagnosed and reported. This has been due partly to a better knowledge and awareness of this syndrome by physicians, and partly to the increasing use of translumbar aortography.

This patient's signs and symptoms were typical of the syndrome, and like many of these patients he was a male in his 40's when his first symptoms commenced. As in many reported

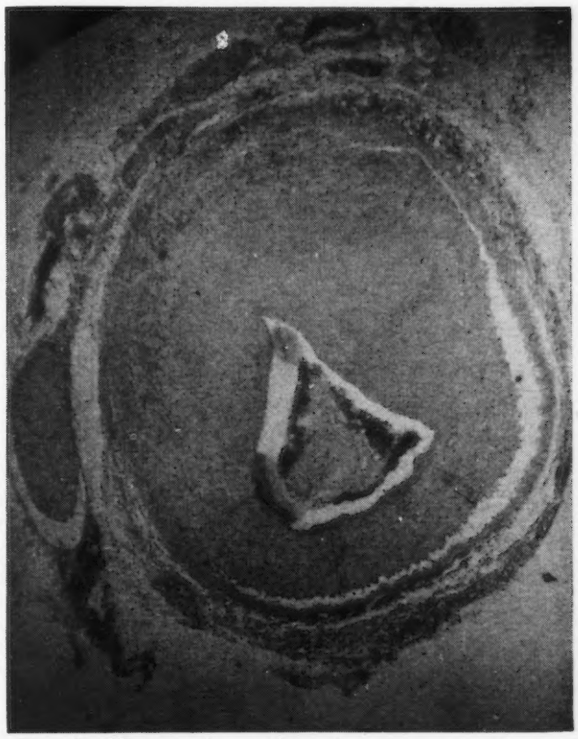

Fig. 6.—Microscopic section of a large renal vessel (left).

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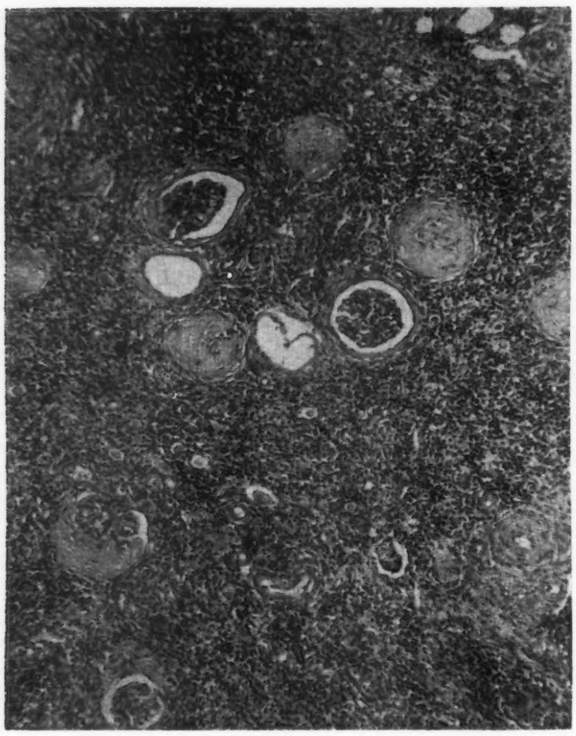

Fig. 7.—Microscopic section of the kidney removed at operation.

cases, his condition was not diagnosed correctly for years. In this instance it took some 14 years after the onset, and some 12 years after he first sought medical aid. Although competent observers attended him, he was labelled as a psychoneurotic for several years.

One of his symptoms that proved misleading in 1941 was upper extremity weakness. The explanation for this is rather difficult unless one theorizes that with ischæmia produced by his thrombosed aorta, enough metabolites were produced constantly so that *any* muscular activity would be inclined to produce fatigue and weakness much earlier than usual.

This patient had weakness and fatigue in the lower limbs and back for two years before he experienced pain. He also demonstrated the important sign of thigh and hip claudication found in lesions involving vessels above the femoral artery.

Impaired or absent pulsations of the femoral vessels should always make one suspicious of the possibility of thrombosis of the abdominal aorta, as well as coarctation of the aorta. It is remarkable how often the femoral vessels are not palpated in the routine examination of patients.

The loss of libido or the development of impotence has not been a universal finding in the cases reported in the more recent literature. It has been said that the testicular arteries have to be involved before this will occur. The aortogram in this case showed thrombosis past the testicular artery up to and including the left renal artery. It also demonstrates the extensive collateral circulation that takes place and accounts for viability of the intra-abdominal viscera, as well as the tissues of the parietes and lower limbs. Quiring[2] in his anatomical drawings (Figs. 9 and 10) shows graphically the chief vessels involved in this collateral circulation.

This case also demonstrates the relative good circulation to the lower limbs, in that there were no significant changes in the skin, nails, or fat pads, such as one frequently sees in the more peripheral type of vascular involvement of the lower limbs. However, this patient had a loss of muscle mass in thighs and the calves.

The value of the stethoscope in listening for bruits in the abdomen is exemplified in this syndrome. The bruit usually is heard above the navel.

Hypertension is invariably present but usually of a moderate degree (systolic and diastolic). This is explained on the basis of increased peripheral resistance at the site of the block. However, should a renal vessel be involved resulting in an ischæmic Goldblatt type

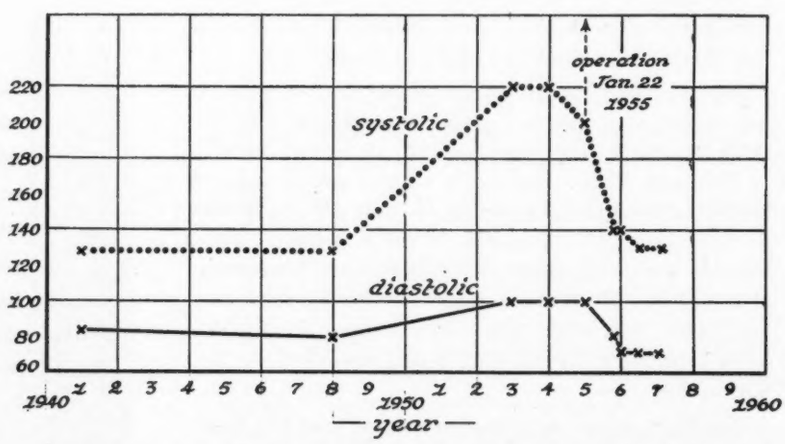

Fig. 8.—Graph of blood pressure readings of this patient from 1941 to January 22, 1955, at the time of the operation, and the subsequent fall in blood pressure to normal levels, remaining so two years postoperatively.

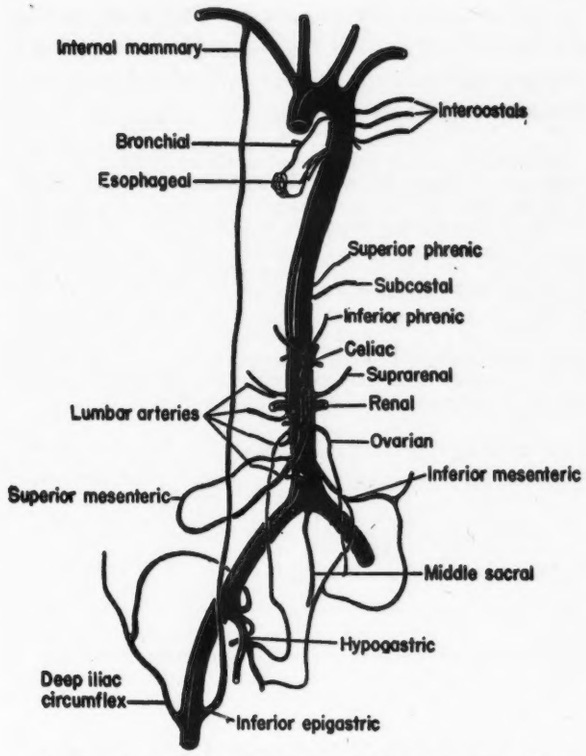

Fig. 9.—The chief tributaries of the aorta. In addition to the direct collateral pathway between the external iliac and the subclavian arteries via the epigastric and the internal mammary, a second by-pass (not shown) is offered by the vertebral, intercostal and spinal arteries.

of kidney, the hypertension can be more prominent.

In trying to assess this case we felt we had one of three choices: (1) Treat the patient medically. (2) Remove the left kidney. (3) Resect the abdominal aorta and replace it with a homograft.

In the hands of De Bakey[3] the latter procedure has proven feasible, as demonstrated by his recently reported series of some 137 cases for aneurysms and occlusive diseases of the abdominal aorta. In occlusive disease of the aorta his operative mortality was 3% (2 deaths).

We felt that medical treatment offered a poor prognosis, as the patient showed evidence of cardiac, cerebral and retinal involvement. His headaches were a constant source of annoyance. If he was going to be improved by any operation, further delay would possibly offer less chance of relieving his blood pressure or his headaches.

We chose nephrectomy, as it carried the lesser risk of the two surgical procedures and offered a good chance of relieving his hypertension and headaches. In spite of the fact that he had had significant hypertension since 1952, at the time of operation he showed good kidney function. Another fact influencing our decision was that his blood pressure was not at a fixed level.

One of the symptoms relieved by his nephrectomy was headache. This was predicted by our surgical colleague Dr. Aberhart, and it became evident the day after operation when the patient was partially ambulant. The patient himself pointed this out to us that day and subsequently. One must consider the possibility of a psychogenic element in the disappearance of the headaches, but we felt it was a spontaneous admission on the part of the patient, and our clinical judgment of the patient at the time was against a purely psychogenic basis. This relief of headache occurred while his blood pressure was still elevated (190/90), and it brings up the question of the pathogenesis of headache in hypertension with a unilateral ischæmic kidney. It would appear that the involved kidney had some bearing on this symptom.

This man is 60 years old now and feels subjectively remarkably improved, although medically speaking he still is in a precarious position, as only a fraction of an inch separates the upper level of this thrombosed aorta and his remaining right renal artery. In his present state of good

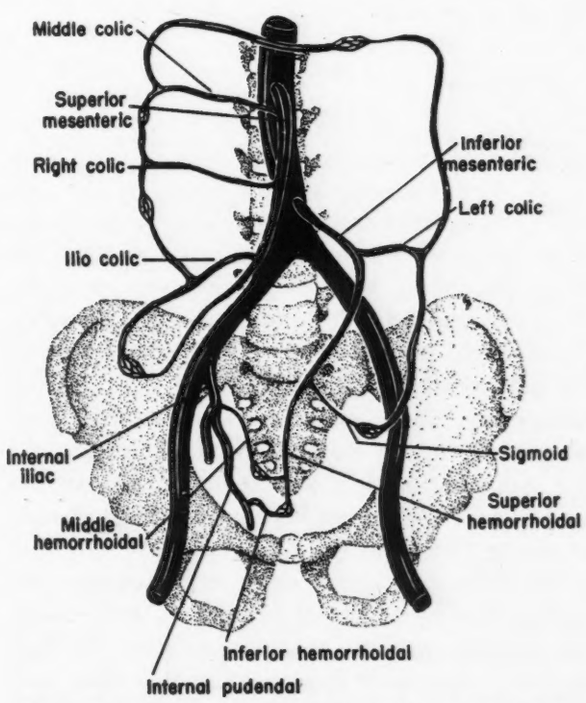

Fig. 10.—Anastomoses of the superior and inferior mesenteric arteries. Note the collateral pathway from the superior mesenteric to the hypogastric artery via the middle colic, the inferior mesenteric and the hæmorrhoidal vessels.

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health he would not consider further surgical intervention such as an aortic graft.

During the past few years, three other cases of thrombosed abdominal aorta have been encountered on the medical service in this institution:

1. A case reported by Spaulding[4] in which the patient died of uræmia. At autopsy the abdominal aorta was thrombosed as high up as and including the renal arteries.

2. The recent case of a 74-year-old patient with bilateral amputation dating back for years. This patient ultimately died of carcinoma of stomach with metastases. At autopsy he had thrombosed iliacs and aorta up to but not including the renal vessels.

3. A case is still on the ward with the following diseases: Marie-Strümpell arthritis, pulmonary tuberculosis and peripheral vascular disease, with impending gangrene. He has no pulsations from the femorals down, as well as leg and thigh claudication. No aortogram has been done on this patient.

In patients dying in uræmia with no pre-existing renal disease, one should consider the possibility of a vascular occlusion such as thrombosis of the abdominal aorta.

The need for bilateral amputation of legs should make one also consider the possibility of thrombosed aorta.

SUMMARY

A case has been presented of thrombosed abdominal aorta with left renal artery involvement. Symptoms apparently began at the age of 41, and presented a problem in diagnosis for many years. It was only after renal involvement produced more significant symptoms that the diagnosis was made by translumbar aortography.

Although transplantation of abdominal aorta by homograft was considered the treatment of choice in these cases, the thrombosis here seemed to be too close to the renal vessels and we believe that left nephrectomy offered the best chance of helping him and the least chance of doing him harm.

To date, two years after nephrectomy, the patient has been free of headaches, and except for a mild cerebral vascular accident, he has shown considerable improvement in morale and general condition. We feel that he had a Goldblatt type of kidney, which was responsible to a large degree for his elevated blood pressure.

The sequence of events in this case would lead us to believe that the ischæmic kidney has a bearing not only on the level of blood pressure, but also on the headaches.

Acknowledgments are due: Dr. C. M. Spooner, Chief Urologist, Toronto Western Hospital, and Dr. H. Waddington, Staff Physician, Toronto Western Hospital, for making the correct diagnosis in this case, and for the use of the aortogram; and to Dr. D. P. Quiring and his publishers, Lea & Febiger, for permission to publish diagrams from *Collateral Circulation*. We would like to thank Dr. A. J. Blanchard, Director of the Department of Pathology at Sunnybrook Hospital, for the pathological sections and their description. We are obligated to the Medical Arts Department at Sunnybrook Hospital for the photographic prints for this paper.

REFERENCES

1. LERICHE, R. AND MOREL, A.: *Ann. Surg.*, 127: 193, 1948.
2. QUIRING, D. P.: Collateral circulation, anatomical aspects, Lea & Febiger, Philadelphia, 1949.
3. DE BAKEY, M. E., COOLEY, D. A. AND CREECH, O., JR.: *J. A. M. A.*, 157: 203, 1955.
4. SPAULDING, W. B.: *Canad. M. A. J.*, 61: 162, 1949.

VASCULAR HÆMOPHILIA IN A WOMAN*

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THE OCCURRENCE in women of an antihæmophilic globulin (A.H.G.) defect associated with a prolonged bleeding time appears to have been first recognized by Alexander and Goldstein[1] and Larrieu and Soulier.[2] In a recent review, Singer and Ramot[3] were able to find 14 other such instances in women and 6 in men. Matter and his colleagues[4] have suggested the excellent name of vascular hæmophilia for this unusual entity. The clinical picture is one of abnormal hæmorrhage from infancy. Bruising, deep tissue, genito-urinary and gastro-intestinal hæmorrhages are common but joint hæmorrhage appears to be uncommon.[3]

Methods.—Standard methods were used for routine hæmatological estimations.[5] Clotting times were determined by a modified Lee and White method (normal 6 to 12 minutes), and the bleeding times are by the method of Duke. Other tests reported are: thromboplastin generation test,[6] prothrombin assay,[7] factor V

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assay,[8, 9] factor VII assay[10] and antihæmophilic globulin assay.[11] This latter test has been modified to use brain extract[12] in place of platelets.

CASE HISTORY:

A. *Family history.*—The father and mother are unrelated and neither has shown abnormal hæmorrhage. The patient's sister, however, has mild menorrhagia. The father was the only relative available for investigation. His clotting time, bleeding time, one-stage prothrombin time, platelet count, clot retraction and thromboplastin generation test were all normal.

TABLE I.

Hb. level 8.6 g.....	Bleeding time	over 15 min.
Red cell count		
5.0 million.....	Clotting time	6 min.
M.C.H.—17 μμg...	Platelet count	527,000
M.C.H.C. 28%...	Prothrombin activity	100%
White cell count		
5700.....	Clot retraction	normal
Differential, normal		

B. *Personal history.*—The patient, Mrs. V.M., aged 24 years, has had pathological hæmorrhagic manifestations since the age of 2. At that time, she had epistaxes and later ecchymoses and purpura but no gastro-intestinal or joint hæmorrhage. This improved during childhood, but when her menses began she had moderate to severe menorrhagia requiring 12 transfusions up to 1954. The patient was first seen at this hospital in 1951 when she received a transfusion as an out-patient. Laboratory results are only available from that visit (Table I).

The patient was next seen at this hospital on January 31, 1954, with antepartum hæmorrhage. She later gave birth to a stillborn infant. Severe postpartum hæmorrhage and hæmaturia developed. Physical examination at this time was normal aside from the pregnancy and accompanying hæmorrhage. During the ensuing three weeks she received 21 bottles of blood, ACTH drip infusions and 625 c.c. of fresh frozen plasma (suggested and provided by Dr. B. P. L. Moore, of the Canadian Red Cross Blood Transfusion Service).

Table II shows in summary the course of this episode. The capillary resistance test, one-stage prothrombin and fibrinogen estimations were repeatedly normal. It should be noted that on two occasions (February 2 and 3) the bleeding time was grossly abnormal in the morning. This gradually returned to normal during the course of the day while she was receiving transfusions of bank blood. These findings occurred prior to the administration of ACTH. Because of two findings of abnormal clotting time (February 11 and 13) but normal bleeding time, a thromboplastin generation test was performed. A defect was apparent in the $Al(OH)_3$ absorbed plasma portion, compatible with an AHG defect. In addition to blood transfusion, fresh frozen plasma was then given with good clinical effect.

In June 1956, the patient was readmitted because of a pelvic mass which appeared to have been a blood clot and which resolved. She was reinvestigated at that time (Table III). In the thromboplastin generation test utilizing equal parts of plasma, the normal corrected a known classical male hæmophilic and the patient. The

TABLE II.

Date—Feb. 1954	*2*	*3*	*11*	*13*	*19*	*20*	*21*	*22*	*24*
Clotting time—min....	8	6	15	13	6				11
Bleeding time—min...	37 2*	30 8 2*	1	2	4				2
Platelet count.....	105,000	370,000	481,000						270,000
Thromboplastin generation test....					Plasma abnormal (22% of normal)				
Abnormal hæmorrhage	←						→		
Blood transfusion.....	←							→	
Fresh frozen plasma...					←		→		
ACTH.....			←					→	

*Normal bleeding time at end of daily transfusion.

TABLE III.

Capillary fragility— normal.....	One-stage prothrombin	100%	
Bleeding time— 18-22 min.....	Factor V assay	100%	
Platelet count— normal on film.....	Factor VII assay	100%	
Clot retraction— normal.....	Two-stage prothrombin	93%	
Clotting time—15 min...	AHG assay	1%-2%	

THROMBOPLASTIN GENERATION

Platelets	*$AL(OH)_3$ plasma*	*Serum*	*Substrate*	*1*	*2*	*3*	*4*	*5*	*6*	*Minutes*
N	N	N	N	41	21	11	9.5	10.5	11	Seconds
P	N	N	N	35	14	8.5	8.5	—	—	Seconds
N	P	N	N	45+	45+	45+	38	35	32	Seconds
N	N	P	N	45+	38	12	8.5	8.5	—	Seconds
P	P	P	N	45+	45+	45	33	27	32.5	Seconds
N	N	N	P	45+	32	13	9	9	—	Seconds
N	H	N	N	45+	45+	45+	43	39	38.5	Seconds
N	H/P	N	N	45+	45+	45+	39	38	36	Seconds
N	H/N	N	N	45+	34	17.5	11.5	10.5	11.5	Seconds
N	P/N	N	N	45+	33.5	18	11	11.5	12	Seconds

N—Normal. P—Patient. H—Male hæmophilic (AHG defect).

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TABLE IV.

Time (hrs.).....	0	2	4	6	8	18
Bleeding time (min.)....	18	9	6	13	28	24
AHG assay (% normal).....	1	1.7	6	1.5	1.4	1.5
Blood/ACD, c.c.....	0	200	400	—	—	—

patient, however, failed to correct the hæmophilic. Assay of her antihæmophilic globulin on two occasions gave levels of 1% and 2% of the average normal levels. Table IV shows the effect of transfusing 280 c.c. of fresh blood in 120 c.c. of A.C.D. solution. The antihæmophilic globulin level was briefly raised to 6% of normal and the bleeding time was moderately improved. Later the patient was given cortisone 100 mg. per day for three days followed by prednisone (Metacortin) 5 mg. q.i.d. for three days and finally ACTH 40 units b.i.d. intramuscularly for three days. All three drugs failed to influence the bleeding time.

DISCUSSION AND SUMMARY

The abnormality of coagulation in this patient appears to be identical with that of classical hæmophilia (AHG defect) in the male. The diagnosis was obscured initially by the normal clotting time, a finding which is not uncommon in this disorder. It would seem that a thromboplastin generation test should be done on all patients with an unexplained prolonged bleeding time even though the clotting time is normal.

A factor present in fresh blood was capable of improving the bleeding time but only for a few hours. A similar transient effect on the antihæmophilic globulin level was also demonstrated. Cortisone, prednisone (Metacortin) and ACTH were ineffective in improving the bleeding time.

The authors wish to thank Dr. A. M. Evans of the B.C. Cancer Institute for the facilities to carry out this investigation and Drs. D. M. Whitelaw, J. Zimmerman, H. J. Van Norden and A. Herstein for referring this patient.

REFERENCES

1. ALEXANDER, B. AND GOLDSTEIN, R.: *J. Clin. Invest.*, 32: 551, 1953.
2. LARRIEU, M. J. AND SOULIER, J. P.: *Rev. hémat.*, 8: 361, 1953.
3. SINGER, K. AND RAMOT, B.: *A.M.A. Arch. Int. Med.*, 97: 715, 1956.
4. MATTER, M., NEWCOMB, T. AND MELLY, A.: *Clin. Res. Proc.*, 4: 53, 1956.
5. PERRY, W. H. AND DEAN, L.: Manual of hæmatology, Vancouver General Hospital, 1954.
6. BIGGS, R. AND DOUGLAS, A. S.: *Brit. J. Clin. Path.*, 6: 23, 1953.
7. BIGGS, R. AND MACFARLANE: Human blood coagulation and its disorders, Blackwell Scientific Publications, Oxford, 1953, p. 353.
8. STEFANINI, M.: *Lancet*, 1: 606, 1951.
9. WOLF, P.: *Brit. J. Clin. Path.*, 6: 34, 1953.
10. OWREN, P. A. AND AAS, K.: *Scandinav. J. Clin. & Lab. Invest.*, 3: 201, 1951.
11. PITNEY, W. R.: *Brit. J. Hæmat.*, 2: 250, 1956.
12. BELL, W. N. AND ALTON, H. G.: *Nature*, 174: 880, 1954.

CONGENITAL ANOMALIES OF THE ANORECTUM

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CONGENITAL ANOMALIES of the anorectal region may be minor and of little consequence. On the other hand, they may be major and of great consequence. A few of the latter type are examples of the meanest tricks Mother Nature plays on her children. The objects of this paper are threefold: first, to refresh in the mind of the reader the developmental anatomy of the region; second, to classify anatomically and symptomatically the various common types of the anomalies; and third, to outline in a general way the management and correction of the various types. The case to be presented serves as an example of the major type complicated by sinus communication to the bladder.

INCIDENCE

The incidence of anorectal anomalies is approximately one anomaly in every 5000[1] newly born babies. The incidence is similar to that of tracheo-œsophageal fistula and is probably half that of hare lip and cleft palate.

EMBRYOLOGY

Embryology gives the clue to the genesis of congenital anomalies. In the human the second month of intra-uterine life is the most significant in this regard. In this eventful month the main facial structures develop and fuse; the diaphragm appears and divides the thorax from the abdomen; and a primitive anus joins a primitive rectum to form the anorectum. An arrest of any one of the developmental processes gives rise to a congenital anomaly. In the case of the anorectum an arrest in the development of the proctodeum at the seventh week gives rise to absence of the anus in part or in whole; an arrest of the development or descent of the hindgut gives rise to a partial or complete absence of the rectum or a failure of it to fuse to the anus; an arrest in the absorption of the anorectal membrane at the eighth week gives rise to imperforate anus or stenosis at the anorectal line; an arrest in the division of the cloaca in the sixth to seventh week results in a sinus between the rectum dorsally and the bladder, urethra or vagina ventrally.

CLASSIFICATION

A convenient anatomical classification of anorectal anomalies is that of Gross.[2]

Type 1—a stenosis of the anus or rectum. The stenosis, as a rule, occurs at the anorectal line and is due to an incomplete absorption of the anorectal membrane. Exceptionally, the stenosis is inferior or superior to the usual level.

Type 2—an imperforate anus, the obstruction being the ano-rectal membrane.

Type 3—an imperforate anus with a rectal pouch ending some distance above the anus. The case to be presented later is one of this type.

Type 4—a normal anus and lower rectum but a deficiency in the mid rectum.

Any one of the above-mentioned types may be complicated by fistula; indeed in type 3, fistula is present in the majority of cases.

SYMPTOMATOLOGY, TREATMENT AND PROGNOSIS

Type 1 cases vary in their clinical picture according to the degree of stenosis. Their symptoms include dribbling of meconium, ribbon-like stools, constipation, bloating and pain on defæcation. Visual or digital examinations reveal the stenoses. Moderate stenoses respond to repeated digital dilatations. The more severe stenoses require incision followed by repeated dilatations. The outlook on the whole is excellent. Occasionally a neglected case of complete obstruction is a real challenge, and only in these cases is there a factor of mortality.

Type 2 cases are, as a rule, detected at birth or within the first day or two of life. The intact membrane may be discovered as the original symptom, but if this anomaly goes undetected, the lack of bowel movements, abdominal distension and vomiting give a clue to the diagnosis. Those anorectal membranes that are thin may be ruptured by the examining fingers; other tougher ones require a cruciate incision. Except for the rupturing or incision of the membrane, the treatment and prognosis are similar to those of type 1 cases.

Type 3 cases are similar to the type 2 in that, as a rule, they are detected at or within a few hours of birth. Occasionally their recognition is delayed until all the classical symptoms of large bowel obstruction become manifest. Radiographs taken according to the method of Wangensteen and Rice[3] assist in determining the distance between the rectal and anal pouches. If the distance is small, one to three centimetres, the anomaly may be corrected by early perineal surgery. If the separation is over three centimetres, the primary operation is restricted to colostomy. The final operation is undertaken months or even years later. The case to be presented later is an example of the type 3 group complicated by fistula to the bladder.

Type 4 cases can be detected at birth, the dome of the lower rectal pouch being easily reached by the examining finger. If the anomaly should go undetected, then in several days the classical symptoms of low intestinal obstruction become manifest – abdominal distension, vomiting and dehydration. A radiograph taken with the infant in the inverted position may indicate the distance between the upper and lower rectal pouches. The initial treatment is directed towards improving the metabolic state of the infant. Operation at this time is restricted to colostomy. The corrective surgery is delayed for 12 months at least. If the defect is small, an anastomosis between the two rectal pouches can be performed from below. If the distance is considerable, the anastomosis is performed through an abdominal incision. The survival rate is high in this group if the infants are seen early and if the surgeons restrict the primary operation to colostomy. On the other hand, the mortality may rise to 50% in a series in which there has been delay in diagnosis and over-enthusiasm on the part of the surgeons. Those who survive operation should be normal in structure and function.

CASE HISTORY

R.R. was born six years ago. At birth the infant was considered to be a normal male. Some hours later, an anorectal anomaly was discovered (Fig. 1) and the infant was transferred to the Children's Hospital under the services of the writer. On admission the abdomen was slightly distended, the anus was imperforate, and meconium and flatus were passed per urethra. Radiographs indicated a distance of three to four centimetres between the anal membrane and the rectal pouch (Fig. 2).

Supportive treatment under the direction of Dr. Harold Stockton, pædiatrician, was administered during the period of investigation. At 40 hours of age the infant was operated upon and a double-barrelled sigmoid colostomy was established.

Postoperative progress was favourable. The proximal loop colostomy discharged fæces and the distal loop passed urine. Dr. John Balfour, urologist, cystoscoped the infant and confirmed the clinical opinion that there was a communication between the bladder and rectum. Dr. Balfour reported that the communication was so large that the rectum

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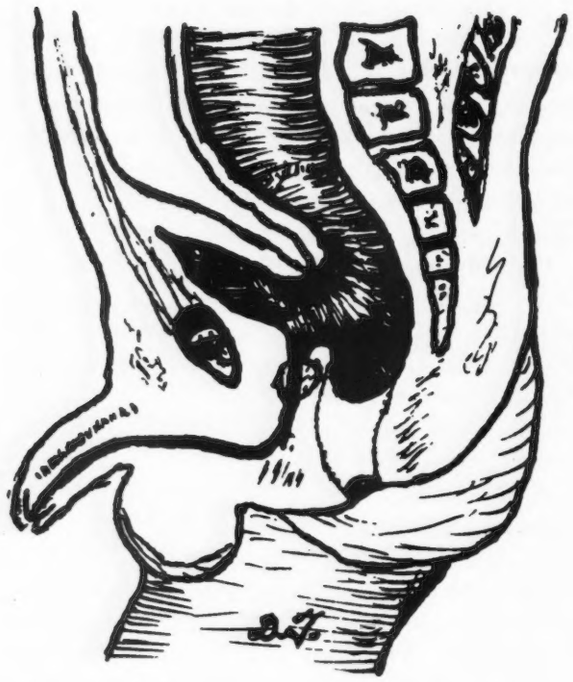

Fig. 1.—Drawing to show the ano-rectal anomaly present in the writer's case. Note the communication between the rectal pouch and bladder.

and bladder formed a cloacal type of cavity. Cystograms confirmed these reports.

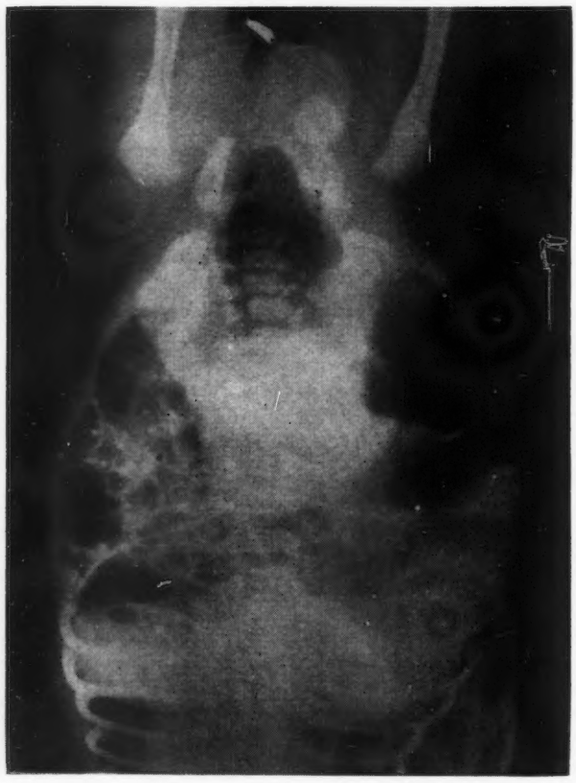

Fig. 2.—Radiograph of the writer's case taken according to the method of Wangensteen and Rice. Note the 3-4 cm. defect between the rectal pouch and the anus.

When the infant was six weeks of age, the distal colostomy was closed, leaving a small segment of sigmoid and rectum attached to the bladder.

The child made an uneventful recovery and was sent home with fæces discharging through the colostomy and his urine passing normally per urethram.

At 13 months of age the child was readmitted to hospital. His general health was good and his weight was 21 lb. After a short period of investigation, he was prepared for the final stage of surgery. At operation the colostomy was closed and the sigmoid, descending colon and splenic flexure were mobilized. Ligation and division of the inferior mesenteric artery at the aorta was performed in order to secure sufficient mobilization. A tunnel was created in the hollow of the sacrum and the bladder with its rectosigmoid appendage was displaced anteriorly. An incision was made in the anal dimple and the fibres of the sphincter ani were identified. Finally the colon was drawn through the anus and a colo-anal anastomosis was established by a pull-through method.

The postoperative progress was uneventful. Special care in the form of repeated dilatations was directed towards the prevention of anal stenosis.

Today R.R. is a vigorous, well-adjusted, intelligent child of six. His colon action is fairly satisfactory although the sphincter control at the anus leaves much to be desired. About once a month the child has "a slip" and soils his clothing slightly. The soiling is usually occasioned by an over-indulgence in fruit. The urine is passed normally per urethram. The urine at first contained considerable mucus, undoubtedly from the segment of rectosigmoid appended to the bladder. At the present only a shred or two of mucus is seen in a urine specimen. There has been no cystitis or pyelitis.

SUMMARY

In this paper the writer has introduced his subject by commenting briefly on the incidence, etiology and anatomy of anorectal anomalies. A simple classification has been submitted in which the anomalies are divided into four types. The symptomatology and treatment has been outlined for each type and a case illustrative of type 3 has been presented.

REFERENCES

1. DAVID, V. C. AND GILCHRIST, R. K.: Nelson new loose-leaf surgery, Nelson and Sons, New York, 1949, p. 141.
2. GROSS, R. E.: The surgery of infancy and childhood, W. B. Saunders Company, Philadelphia, 1953, p. 349.
3. WANGENSTEEN, O. H. AND RICE, C. O.: *Ann. Surg.*, **92**: 77, 1930.

SHORT COMMUNICATIONS

MECHANICAL HEART MASSAGER*

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CARDIAC ARREST occurs not infrequently during the course of general surgery and cardiac surgery. Many factors which may precipitate the onset of cardiac arrest are beyond the scope of this article. When cardiac arrest occurs, it is imperative that blood be sent to the brain and other vital organs within three minutes. To accomplish this, the heart has either to be started again or manual massage begun. When manual cardiac massage is properly performed it is possible to resuscitate an arrested heart and keep the patient alive while the heart is being revived.

Experience has shown that there are great variations in the ability of different surgeons to obtain a satisfactory blood pressure from manual cardiac massage. Sometimes the heart may be restored but because of inadequate cerebral circulation during the period of massage the brain suffers irreparable damage and the patient dies.

In other instances the surgeon is able to maintain proper cerebral blood pressures but the heart fails to revive and manual massage has to be discontinued because of fatigue. Such was the situation in October 1955, when a patient suffering from angina decubitus caused by coronary artery disease was given an anæsthetic for internal mammary artery implantation.

When the left chest was opened there was a sudden onset of left ventricular fibrillation and the heart stopped. The pericardium was quickly opened and defibrillation accomplished. Manual heart massage was then performed continuously for eight hours, at the end of which time the patient was still alive. During the hours of manual massage the blood pressure was maintained at 60 mm. Hg or better and the patient required the intermittent administration of nitrous oxide to keep him asleep. Unfortunately the heart did not revive.

This man was kept alive by a pair of hands. His life was literally in the hands of the operator. Each time the surgical resident attempted massage there was no blood pressure and the pupils became dilated. At the end of eight hours manual massage was discontinued because of fatigue, and the patient died.

This was a most disturbing experience, particularly since the patient was alive until the last minute, requiring nitrous oxide to keep him asleep. The autopsy failed to show any evidence of a fresh coronary occlusion or infarction. If cardiac massage had been more adequate and could have been maintained longer, there is a possibility that such a heart might have recovered. After this experience, work was begun upon a mechanical apparatus adapted to apply resuscitation and massaging action to the human heart.

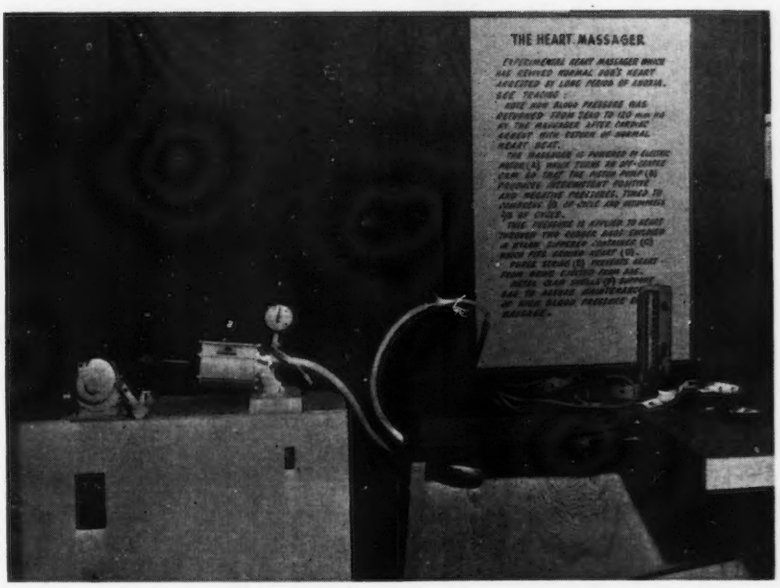

Fig. 1a.—Photograph of mechanical heart massager displayed at Canadian Medical Association Annual Meeting, June 1956. On the table the part which fits around the heart surrounded by metal cups is shown surrounding a balloon which was attached to a sphygmomanometer, showing a type of pressure obtainable when the massager was demonstrated.

The apparatus to be described has two major parts, the mechanical massager and the pumping power unit.

1. *Mechanical massager*—The part of the mechanical heart massager which has been the most difficult to design is the part applied to the heart. The shape of the heart makes it difficult to apply mechanical pressure without damaging the myocardium or coronary vessels. In June 1956 the apparatus was exhibited at the Annual Meeting of the Canadian Medical Association (Fig. 1a).

The main element of the apparatus consists of a flexible pouch or sac (10) which is provided along one side with a zipper closure (12) and along the open top with a drawstring (14). A pair of flexible diaphragms (16a) (16b) are sewn to the interior walls of the flexible pouch (10), so as to constitute an airtight flexible

*From the Department of Experimental Surgery, McGill University.
The pumping mechanism was planned and made by Electrodesign, Montreal.

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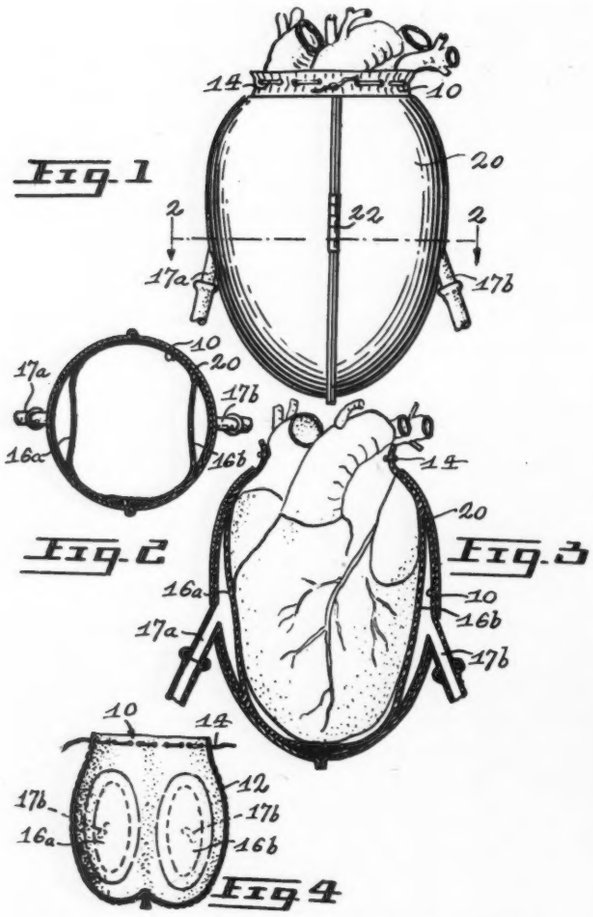

Fig. 1.—Metal shells were used at first to maintain pressure on heart. These were difficult to apply and subsequently found not to be necessary. Fig. 2.—Cross-section of construction of sac and diaphragms. Fig. 3.—Vertical sections of sac and diaphragms. Fig. 4.—Sac opened, showing position of flexible diaphragms and purse string.

membrane which can be expanded or contracted by the application and release of fluid pressure, i.e. air. The material used for the sac was nylon and the flexible membranes were made of rubber. The membranes (16a) (16b) are connected to conduit portions (17a) (17b) which are attached to the source of fluid pressure. In use the sac or pouch (10) was placed beneath the heart; that is, one side was placed beneath the heart and the other side folded over by the zipper closure (12). The sac envelopes the heart as shown in Fig. 3. The open top is constricted through the use of a drawstring (14) so as to prevent a portion of the heart being forced out through the top when pressure is applied.

In order to exert the pressure applied by the flexible membranes (16a) (16b) against the walls of the heart, the pouch (10) was surrounded by a hollow shell (20) made of rigid material. This was shaped to follow the heart contour. The shell (20) as it was at first was hinged but later was made of two separate halves which were held together by clamps. The ends of the conduit (17a) (17b) pass through suitable openings provided in the walls of the shell (20) where pulsations of fluid pressure are applied through the membranes (16a) (16b). Because of the rigid nature of the outer shell (20) the pressure in the membranes is directed against the walls of the ventricles individually and simultaneously. By this apparatus it was possible to maintain blood pressure and revive the animals' hearts which had been arrested by stopping the artificial respiration pump. The outer shells were difficult to apply and in some animals there was difficulty with venous return because of constriction at the base of the heart caused by the metal shells. Because of this a complete revision of the massaging part of the apparatus was carried out (Figs. 4a and 4b). It was realized that the metal cups were not necessary if smaller diaphragms were made.

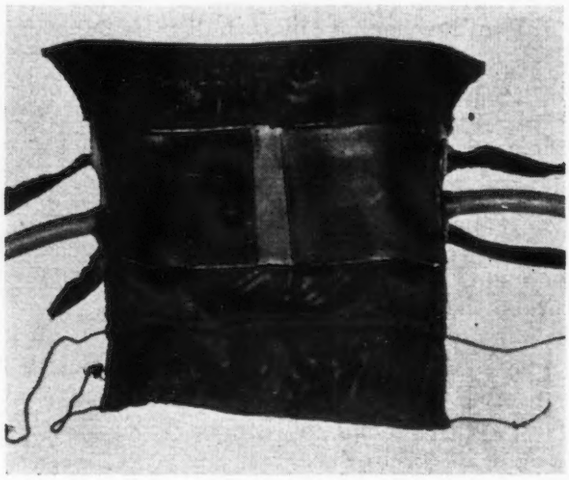

Fig. 4a.—New massager showing 2"-square siliconised rubber diaphragms connected by a piece of rubber placed on the inside of nylon cloth which has drawstrings at both ends; nylon cloth strips on its opening sides are used to tie the massager in position. Attached to the outer surface of the flexible diaphragms are similar conduits as shown in Figs. 1, 2 and 3.

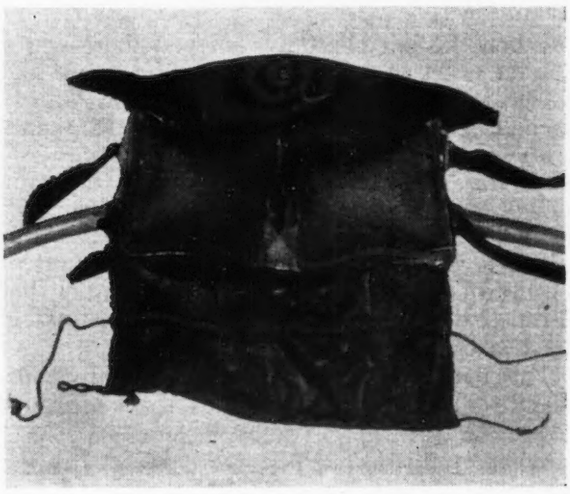

Fig. 4b.—Diaphragm inflated.

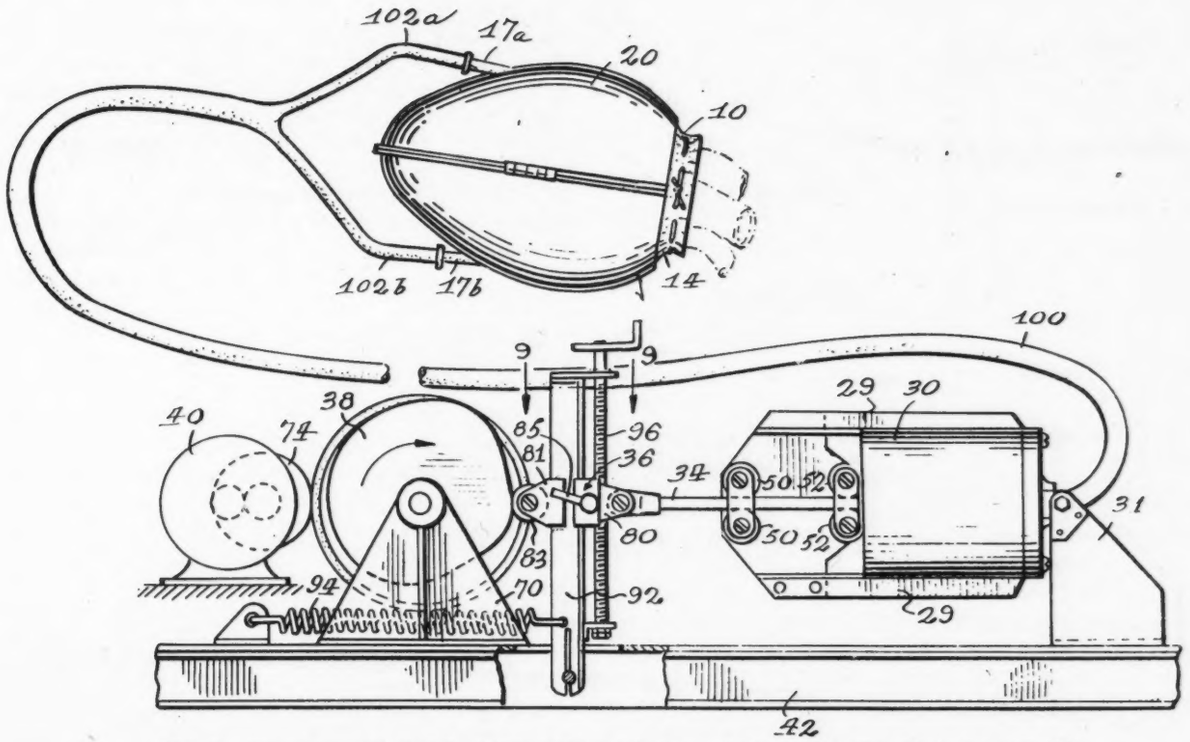

Fig. 5.—Diagrammatic sketch showing the mechanism of the pump—the off-centre cam (38) which permits a one-third compression stroke of piston (30) and two-thirds diastolic stroke run by an electrical motor.

The sac is made of non-stretchable cloth, nylon, open at the top and bottom and on one side. The top and bottom parts are controlled by drawstrings after the sac is placed around the heart. The open part of the sac is closed by tying the strips of non-stretchable cloth attached to the wall of the sac on each side of the opening. Sewn to the *inside wall* of the sac are two 2″-square rubber diaphragms which are connected to the same conduit as in the original massager. By placing the diaphragm on the inside of the non-stretchable sac it has been possible to do away with the hollow metal shells (20) used in the original apparatus. This model can be quickly applied to the heart and is adjustable to hearts of different sizes. Further, it is easy to open it, apply defibrillating electrodes and, when defibrillation has been accomplished, quickly close the sac and resume mechanical massaging. It is planned in later models to incorporate defibrillating electrodes in the walls of the sac.

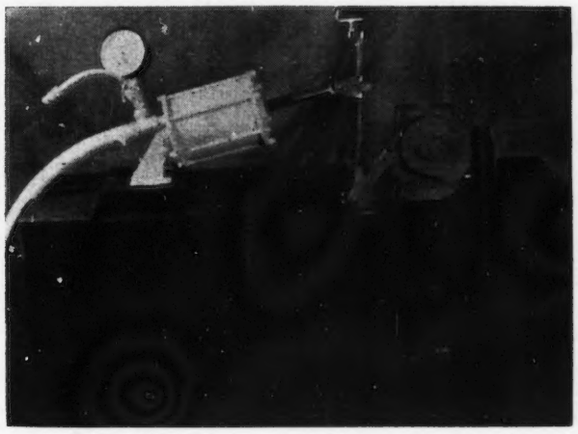

Fig. 5a.—The pumping mechanism mounted. The off-centre cam is shown to the right and the compression cylinder in white to the left.

2. *Pumping mechanism* (Figs. 5 and 5a)—The pulsating fluid pressure supplied to the interior of the flexible diaphragms is produced by means of a double acting air pump having a direct connection to the conduit leading from the flexible diaphragms. The double acting air pump is controlled by a cam (38) having a predetermined contour so that the pressure fluctuation of the flexible diaphragms is divided into: (1) a one-third pressure stroke, and (2) a two-thirds suction stroke per revolution, which corresponds to the one-third systolic contraction and two-thirds diastolic relaxation of the normal heart cycle. The speed of the pump can be varied (see Fig. 5).

TEST OF MECHANICAL HEART MASSAGER

In medium-sized dogs the blood pressure has been recorded continuously on a drum by canulasition of the carotid artery. The left thorax is opened and the artificial respiration pump stopped. The course of the blood pressure as recorded is shown in Fig. 6. Anoxia at first causes the blood pressure to rise, and then it gradually falls until the heart ceases to beat.

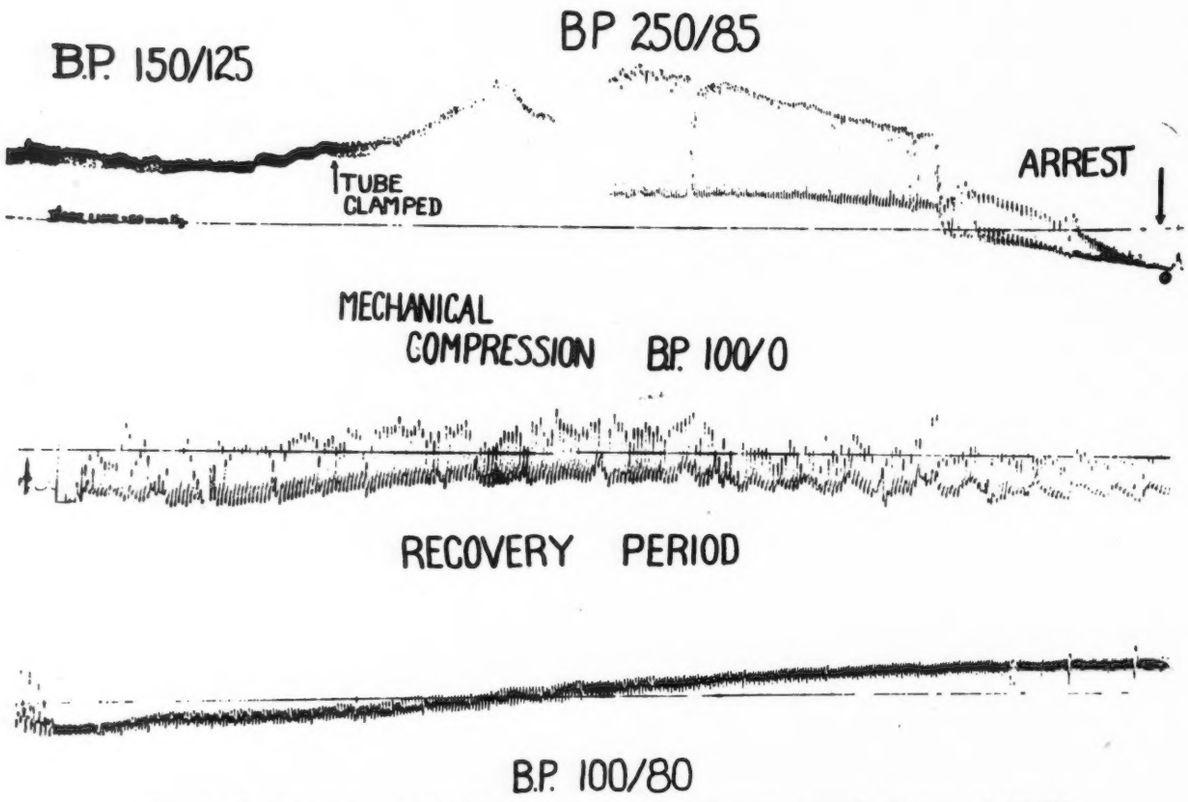

Fig. 6.—Record of the carotid blood pressure of dog showing a blood pressure of 150/125. Baseline was 50 mm. Hg. Artificial respiration tube was clamped. Blood pressure rose to 250/85 and finally dropped to zero with cardiac arrest. Ten minutes after the commencement of anoxia and two minutes after total arrest, mechanical compression of the heart was started, with return of blood pressure to 100. During the massaging the blood pressure was maintained between 60 and 100. Fifteen minutes after commencement of massaging, the heart re-started with return of blood pressure to 100/80, and complete recovery of animal.

This takes about eight minutes. Two minutes after there has been no recorded blood pressure, with no evidence of heart beats (usually from 8 to 10 minutes after the starting of the anoxic period), the cardiac massager is applied to the right and left ventricles through an open pericardium. The effect of the cardiac massager on the blood pressure is immediate. It has been possible in all animals to maintain a blood pressure above 80 mm. Hg. The blood pressure can be kept at this level without difficulty until the heart starts to beat, as has happened in all five of the animals thus treated. All have had complete recovery. In one instance the heart was massaged 15 minutes before it started to beat again. In no case has there been any evidence of coronary artery, myocardial or gross epicardial damage. The shape of the myocardial massager with its 2″ square inflated diaphragms corresponds roughly to the surface of the palms of the hands, which are frequently used during manual massage.

This is a preliminary report. Much more study on animals must be carried out and further refinements have to be made on both the massager and the pumping mechanism. However, it is now safe to say that an arrested heart may be massaged by a mechanical apparatus which maintains an adequate blood pressure during the period of cardiac resuscitation resulting in a return of cardiac action and survival of the animal.

STUDY OF BLOOD CHOLESTEROL LEVELS IN OBESE DIABETICS USING PHENMETRAZINE (PRELUDIN)*

ROSARIO ROBILLARD, M.D. and ROBERT SAUCIER, M.Sc., *Montreal*

BLOOD CHOLESTEROL is a factor worthy of consideration in the problem of diabetes mellitus. Hypercholesterolæmia is often implicated in the degenerative complications of diabetes. One is concerned about the fact that the percentage of diabetics with degenerative complications is the same as that of diabetics with hypercholesterolæmia, namely about 85%.

*From St. Luke's Hospital, Montreal.

The frequency of hypercholesterolæmia in uncontrolled diabetes seems to be accepted by all. However, opinions are still divided as to which is the most efficient method of reducing the blood cholesterol level. It would be an overstatement to assert that we are totally helpless in the case of hypercholesterolæmia or that even the complete removal of cholesterol and fatty substances from the diet produces only a slight drop in its level. It would seem equally exaggerated to play down the value of the success obtained by low calorie and low cholesterol diets in reducing the hypercholesterolæmia of diabetics and thus giving the credit only to insulin as certain advocates claim. Undoubtedly, hypercholesterolæmia is partly due to a diet rich in fat and cholesterol, but we must admit that hypercholesterolæmia has an endogenous origin in diabetics. It would be beyond the subject of this paper to stress this endogenous origin. However, it may be said that endogenous cholesterol can stem from carbohydrates or proteins and that hormones, particularly ACTH, and a deficiency of thyroxine can increase the production of cholesterol by the body.

The variations of blood cholesterol levels in diabetics submitted to weight reduction with phenmetrazine was the subject of this study. Our only objective was to study the effect of weight reduction on blood cholesterol levels, because we have no proof that this drug has a hypocholesterolæmic effect.

In order to have results acceptable from the scientific point of view, we could not be satisfied with the method of estimating the blood cholesterol used in the clinic. We therefore used the method for cholesterol level determination published by Schoeheimer and Sperry.[1] This method consists of extracting the cholesterol by means of an acetone-alcohol mixture, followed by hydrolysis of the esterified cholesterol. Cholesterol is precipitated by digitonin and estimated colorimetrically with the Liebermann-Burchard reagents. The normal blood cholesterol values by this method are between 150 and 250 mg. %.

We have studied nine obese diabetics and have recorded their weight loss in relation to the maximal fall in blood cholesterol level (Table I).

These results suggest that this reducing diet was able to bring about a fall in blood cholesterol levels, but we were unable to establish a direct relationship between the amount of weight lost and the fall in the blood cholesterol level (correlation coefficient r = + 0.486).

What has deceived us mostly is the variability in the cholesterol blood levels in the course of weight reduction. There are many causes of fluctuation in the blood cholesterol level, of which weight loss is one. Those obese diabetics were on a diet of 1210 calories containing 50 grams of fat and 58 grams of protein. We did not take into account the cholesterol content of the food ingested, which might explain in part the relative success obtained in this third stage of the investigation.

TABLE I.

Name	*Weight in lb.*	*Loss of weight (lb.)*	*Blood cholesterol level, mg. %*	*Reduction of blood cholesterol level, mg. %*
Lar.	182 - 171	11	288 - 220	68
Cyr.	192 - 183	9	208 - 160	48
Ben.	160 - 129	31	128 - 64	64
Vin.	209 - 202	7	170 - 139	31
Lan.	203 - 199	4	200 - 150	50
Bru.	237 - 213	24	174 - 151	23
Cad.	204 - 200	4	122 - 107	15
Leb.	165 - 138	27	219 - 128	91
Tho.	226 - 210	16	212 - 150	62

In conclusion, we must admit that although the question of blood cholesterol levels is of great importance and carries serious consequences, its complexities are still unsolved.

Phenmetrazine is the best anorexigenic agent[2] produced so far for use in weight reduction. However, even with these encouraging results the blood cholesterol level remains such a variable factor that no claim can be made for phenmetrazine's correcting at the same time body weight in obesity and high blood cholesterol levels.

The authors are grateful to Miss Diane Roy for her helpful technical assistance. Preludin (phenmetrazine hydrochloride) used in this trial was kindly supplied by Geigy Pharmaceuticals. The diabetics in this trial are treated in the medical service of St. Luke's Hospital.

REFERENCES

1. SCHOEHEIMER AND SPERRY: *J. Biol. Chem.*, **106**: 745, 1934.
2. ROBILLARD, R.: *Canad. M. A. J.*, **76**: 938, 1957.

RÉSUMÉ

Il faut voir dans la question du cholestérol sanguin un problème d'une grande importance et d'une étendue considérable dont la complexité reste encore irrésolue.

La phenmetrazine a réussi, sans complications, mieux que tout autre anorexiant dans les cures d'amaigrissement, mais même avec ces résultats, la cholestérolémie reste trop fluctuante pour faire d'une pierre deux coups: réduction de l'obésité d'une part et correction de l'hypercholestérolémie d'autre part.

WHO WILL OPERATE?

"There seems to be a certain apprehension on the part of some patients that someone other than the surgeon with whom they have consulted will perform the operation. I do not know the basis for this attitude. I do believe, however, that when a patient comes to me and I advise operation – and make the necessary arrangements–I automatically assume the moral responsibility of performing the definitive portion of the operation unless some other arrangement is made with the patient".–L. S. McKittrick, *New England J. Med.*, **256**: 1211, 1957.

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CRITICIZING THE CURRICULUM

As the late and unlamented Dr. Goebbels so successfully demonstrated, if a statement is made sufficiently often and sufficiently loudly it tends to pass imperceptibly into the body of human wisdom. Of recent years there has been a great deal of criticism of the medical curriculum and of its products—sometimes from within the profession, sometimes from outside. Some criticisms of the system and suggestions for its improvement have been heard so often that one tends almost to think of them as true and unchallengeable statements. It is refreshing to read in a recent issue of the *Journal of the American Medical Association** a number of papers which were delivered at the 53rd Annual Congress on Medical Education and Licensure in Chicago last February. For in these pages the criticized turn upon their critics and pour scorn on some of the criticisms and suggestions for improvement of the curriculum.

There seem to be three types of criticism, all of which are discussed in detail in these pages. First, medical schools are accused of training specialists rather than physicians for the general care of patients. Second, they are accused of turning out a product lacking in human understanding, a person whose warm and kindly instincts have been eradicated by too close an acquaintance with details of technology. Third, they are accused of failing to stimulate a medical student's understanding of social, economic and environmental problems affecting health.

In the present series of articles, Weiskotten indignantly repudiates the charge that the medical schools are training specialists. The medical schools find themselves faced with a world in which the immense accumulation of knowledge has produced specialism; they cannot alter this fact, nor is the situation likely to change. Another contributor, Wood, points out the situation very aptly by contrasting the simple, superficial, but world-shaking studies of Wunderlich in his work on thermometry published in 1862 with the deeply involved studies of Puck on the genetics of individual mammalian cells published last year. Medical education is basically designed to produce what Weiskotten calls "an undifferentiated physician" rather than an embryo specialist or an embryo general practitioner. Cope shows in a contribution on integration and correlation that this huge body of accumulated knowledge has transformed the training of a surgeon at Harvard from a one-year course in 1850 to a 14-year course at the present time. If the process continues, by 1970 the surgeon will require 18 years for his training. The only solution for this situation, which is bordering on absurdity, is to ruthlessly jettison unnecessary detail during the training period.

Several contributors take up the other two major criticisms of medicine. At the outset, Weiskotten suggests that we should not pay too much attention to ill-informed criticism from those with no first-hand information on educational programs, and in particular those "who live in a world of words and phrases" not listed in the medical school curricula. Atchley mentions the three attributes of a physician—culture, compassion, and the scientific attitude. The job of the medical school is to inculcate the scientific attitude. The student should have some acquaintance with general culture before he enters medical school, and compassion or sympathy is a quality which is certainly not teachable in the university. Whitehorn comments, in his paper on the orientation of medical students towards the whole patient, on the fallacy that it is possible to teach students to understand human nature and apply such understanding, whereas the primary task is to mobilize the students' innate fund of commonsense. Atchley attacks the widespread impression that a scientific training dries up the milk of human kindness. He says "I have observed many scientific-

**J.A.M.A.*, June 1, 1957, pages 533-552.

ally trained clinicians and also men less lucky in that respect, and I have never seen a sympathetic person frozen by a research career or a cold, tactless individual thawed by general practice". In insisting on the paramount importance of cultivation of the scientific attitude, he notes that the joy of understanding conveyed by science is both the closest rival of the joy of service and its most effective partner.

Much has been said about bringing the student into the patient's home, but some objections are raised in this symposium to his premature introduction into the family sphere. Whitehorn observes that the patient may reveal more to the student in the student's own setting, i.e. the hospital, and that the student himself may feel more at ease in the latter. Atchley is also against dilution of a curriculum with home visits. It is not the photographic impression of the patient's environment that counts, but the patient's attitude to his environment, which can be elicited perfectly well away from the home.

Weiskotten sums up his views on the present situation by suggesting that undergraduate medical education be left in the hands of the medical educators, since these experienced members of medical faculties are best able to evaluate and deal with the complex problems involved. He does advocate, however, that medical educators should draw nearer to organized medicine and be more active in it.

After reading what the medical educators have to say in defence of their work, one is left with the impression that perhaps some of the criticisms advanced against them are exaggerated. Everyone will agree that the present level of medical care is higher than ever before; this care is being given by the men trained by the medical schools. It is much more likely that it is being given *because* of their sound training rather than *in spite of* that training.

Editorial Comments

SALMONELLOSIS

Salmonellosis has become a public health problem of such importance that its control can be achieved only through the concerted efforts and fullest co-operation of clinicians, epidemiologists and bacteriologists.

Two closely related papers have appeared recently containing interesting statistics and observations derived from 16-year studies of salmonellosis. MacCready, Reardon and Saphra[1] analyze the frequencies and seasonal trends of incidence and other characteristics of 2625 salmonella organisms (excluding *S. typhi*) isolated in Massachusetts, and also comment on clinical aspects of the resulting infections. Saphra and Winter[2] evaluate the clinical manifestations of 7779 cases reported mainly from five eastern states, including Massachusetts.

In the investigations, salmonella organisms were recovered mainly from stools, while other sources included blood, spinal fluid, other tissues, food and animals. Of some 50 types identified, *S. typhimurium* was recovered by far the most frequently among all salmonellas other than *S. typhi;* in both studies, this type accounted for over 30% of the infections.

Cases were reported for every month of the year, the peak occurring in August when warm weather encouraged rapid multiplication of pathogens in contaminated non-refrigerated food. The seasonal variation in recovery of *S. typhi* closely paralleled that of the other salmonellas. Young children were much more susceptible to infection than adults, the infection rate being specially high in the first year of life.

Several of these outbreaks were traced to a wide variety of contaminated foods. For instance, one outbreak cited was attributed to lemon pie which had been left standing at room temperature for several hours, another to chopped liver handled by a carrier and still another to sliced watermelon which might have been contaminated by a knife bearing salmonella organisms. Two outbreaks in nurseries were traced to contaminated fluid in the water trap of the delivery-room resuscitator.

The most frequent clinical manifestation was gastroenteritis, which characterized over two-thirds of the cases in both studies. It ranged from the mildest ambulant forms to a most severe cholera-like type with rapid dehydration, convulsions and death, or a dysentery-like form with bloody, slimy discharges and tenesmus. In most patients, the symptoms started 12 to 48 hours after ingestion of contaminated food and lasted one or two days.

The septic syndrome, which was present in less than 10% of cases in both studies, was characterized by fever, often the only clinical sign. In contrast to the fever caused by *S. typhi*, there was generally a high pulse rate and elevated white cell count. Diarrhœa, if present, was mild and of short duration.

Focal infections included appendicitis, cholecystitis, abscesses, pneumonia, meningitis, osteomyelitis and urinary tract infections. Most of these conditions were acute and *S. typhimurium* was frequently identified as the causative agent. There were 20 cases of subacute bacterial endocarditis, 13 of which were due to the highly

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virulent S. *cholerae suis* and 4 to S. *typhimurium;* all these cases had a rapidly fatal outcome.

While temporary convalescent salmonella carriers are frequent, permanent carriers of organisms other than S. *typhi* are uncommon. The fatality rate, which rose steeply in the older age group, was 4.1% for cases reported to the New York Center—about three times that shown in the Massachusetts report. In both studies, the greatest number of deaths followed infection by S. *typhimurium* and S. *cholerae suis.*

Evidence submitted clearly indicates that there has been a steady increase in salmonella infections other than S. *typhi,* particularly in the the past five years. In Massachusetts, for example, 58 cases were reported in 1950 and 393 in 1955. Although more complete reporting may account for part of the increase, a significant part is real and there are no grounds for complacency. This situation contrasts sharply with the marked decline in S. *typhi* infections; in Massachusetts, from 99 in 1940 to 15 in 1955.

It seems apparent that adequate measures must be taken to ensure bacteriological safety of meat, poultry, fish and dried egg powders, the products which are responsible for the vast majority of these infections. L.A.C.

REFERENCES

1. MACCREADY, R. A., REARDON, J. P. AND SAPHRA, I.: *New England J. Med.,* 256: 1121, 1957.
2. SAPHRA, I. AND WINTER, J. W.: *Ibid.,* 256: 1128, 1957.

ATRIAL SEPTAL DEFECT

Patent ductus arteriosus, once relegated to the pathology museum, is now routinely corrected surgically. Atrial septal defect is rapidly falling into this same pattern. It is the most common single congenital heart malformation seen in practice today. In contrast to most congenital heart defects, many cases are first seen in the young adult group.

The anatomical variations are many, but three main types are usually described: (1) atrioventricular defects (persistent ostium primum); (2) fossa ovalis defects (persistent ostium secundum); (3) superior-caval defect (sinus venosus defect). About 10% of cases will have an associated mitral stenosis, while a further 10% will have anomalous pulmonary veins entering the right atrium.

The physiological effect is a shunt of arterial blood from the left atrium to the right atrium, so that pulmonary blood flow is 2-4 times the systemic blood flow. Pulmonary artery pressure remains at or near normal, and there is no cyanosis. Eventually pulmonary artery thrombosis progresses to cause a gradual rise of pulmonary vascular resistance. Then the shunt through the defect will be diminished, balanced or reversed. A clinical picture of pulmonary hypertension and arterial desaturation results.

Many cases will be asymptomatic until the consequences of continual overloading of the right ventricle become apparent. Exertional dyspnœa is followed by right heart failure. Auricular fibrillation and cyanosis may develop. By 40 years of age, over half of the patients will have gross cardiac enlargement.

In such a lesion, which pursues a benign course until the patient is at least 20 years of age, one must balance the risk of operation against the natural history of the disease. The latter was reported by Campbell in a study of 100 cases:[1] "After infancy has been passed, the first two decades are a good period when the patients lead a life that is nearly normal but generally without active games. We think that 95% are still doing well when they are 20, and 85% when they are 30 years of age. The prognosis in the fourth and fifth decades is much less good, and only about half of those seen at hospital are still well at 40, and less than a quarter at 50 years."

Surgical treatment is still in a state of flux. Wood[2] expressed the view that "Until the mortality is under 5%, uncomplicated cases with 2:1 shunts should certainly be left alone." The success of the procedure depends greatly upon accurate diagnosis, and careful selection of cases. With ostium secundum defects and the skilful use of hypothermia, this low rate should be achieved.[3] Ostium primum defect is a much more complex surgical problem, which usually requires more time than is available under hypothermia. Open heart surgery by means of a pump-oxygenator is the present answer to the problem, carrying a high mortality (probably 25-50%).

Pulmonary hypertension and its associated phenomena remain the great contraindication to operation. The severity depends directly upon pulmonary vascular resistance in relation to pulmonary flow. Both of these estimations are difficult to do well, and like any laboratory test must be evaluated in the light of the clinical picture. Bedford and his colleagues[3] found about one-third of cases to be unsuitable for closure under hypothermia.

In summary, atrial septal defect of the ostium secundum type is a lesion which will produce serious disability in over one-half of cases by 40 years of age. Early closure by direct suture under hypothermia is being established as a safe, reliable procedure, with a mortality rate of about 5%. Ostium primum defects are a much more complex surgical problem and carry a higher operative mortality.

R. O. HEIMBECKER.

REFERENCES

1. CAMPBELL, M. AND NEILL, CATHERINE: *Brit. M. J.,* 1: 1375, 1957.
2. WOOD, P.: Diseases of the heart and circulation, 2nd ed., Eyre & Spottiswoode, Ltd., London, 1956.
3. BEDFORD, D. *et al.*: *Lancet,* 1: 1255, 1957.

THE POLICY OF THE HEART FOUNDATION OF CANADA

The provincial Heart Foundations from British Columbia to Quebec are federated in the National Heart Foundation of Canada. It is hoped that in the relatively near future a foundation of the Atlantic Provinces will be established also. The National Heart Foundation gives co-ordination at a national level to the provincial programs of research and education in the relief of cardiovascular disease.

Since the problem of heart disease arises in over half the cases seen by the physician in general practice, it is obvious that the responsibility for the care of such patients lies in his hands. The basis of the program of the Heart Foundations of Canada rests on this premise. They do not plan to undertake individual patient care or treatment; they do not intend to build buildings to compete with existing facilities across the country. From a relatively short but firmly established experience they are confident that their policy is one well adapted to stimulate a background of interest in cardiovascular diseases that will steadily assist the general practitioner, the internist and those concerned with research.

The research program will complement existing research facilities through the support of research personnel and grants in aid of research or of whole units in the field of cardiovascular diseases. It will also provide a training ground for future cardiologists.

Educational programs are both professional and lay. The professional program makes available to the practising doctor booklets, reprints and other literature to help him keep abreast of the recent advances in such fields as the management of congenital, rheumatic, coronary or arteriosclerotic heart disease. Visiting teaching teams organized by the Foundations and sponsored by the local medical societies have held clinics on heart diseases in various parts of the country. These have proved popular, as have refresher courses in the university centres also organized by the Foundations. Both of these activities will continue to be among their important functions.

The lay program will function primarily through the doctor's office. Pamphlets are available to the doctor explaining hypertension, coronary atherosclerosis, heart disease in pregnancy, heart disease in children, and problems the doctor wishes to elucidate in general terms to his patient or relatives. Films and speakers for Service clubs, parent-teacher groups and other organizations are also available.

In summary, the Heart Foundations of Canada will operate within the orbit of and support of the medical profession and its research facilities. The co-operation of all physicians in Canada is earnestly sought.

JOHN D. KEITH, M.D., President.

YOUR SAVINGS FOR RETIREMENT

Previous reports on the Canadian Medical Retirement Savings Plan have described its structure as a split-funded arrangement whereby members may invest their tax-deferred savings in:

(a) a deferred annuity

and/or

(b) a common stock fund

After canvassing all possibilities the Committee on Income Tax has recommended, and the Executive Committee has authorized, the appointment of The National Life Assurance Company of Canada as the carrier of the annuity portion and The Royal Trust Company as trustee and manager of the common stock fund. Arrangements are being made with the Bank of Montreal to accept members' contributions at any of the bank's branches in Canada.

A great deal of work has been accomplished in negotiating the terms of the agreements with the carriers and application for registration of the two elements of the plan has been made to the Department of National Revenue.

Completely descriptive literature has been prepared and this material, with application forms for membership in the Canadian Medical Retirement Savings Plan, will reach you with your Journal in September.

This is a group plan which offers to the doctor member the financial advantage of large-scale financing together with remarkable flexibility in planning his retirement savings. Do not commit yourself to any individual scheme before you examine The Association's plan.

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Medical News in brief

CHLORPROMAZINE AND RESERPINE AND MYOCARDIAL DAMAGE

In a report to *Science* (126: 24, 1957) Bulle of Washington, D.C., reports some animal experiments which suggest that chlorpromazine in very low dosage prevents the myocardiotoxic effect of histamine or serotonin. The experiments were conducted because there is a possibility that histamine and serotonin might be liberated in myocardial infarction and cause damage to the muscle. It remains to be seen whether further experiments will show that chlorpromazine might be of use as an adjuvant in prophylactic treatment of myocardial infarction.

PHYSICAL AND MENTAL HANDICAPS AFTER DISTURBED PREGNANCY

Statistics are produced by Stott of Bristol, England, (*Lancet*, 1: 1006, 1957) to show that physical or mental stress in pregnancy may produce in the infant a syndrome of early ill health, mental retardation and congenital malformation. Stott studied a group of 102 retarded children and found that in the pregnancies that had produced them there were 24 instances of maternal illness, of which 12 were toxæmias, and 48 instances of severe mental stress, such as severe matrimonial trouble, shocks and accidents and anxiety states. There was a close association between maternal illness and stress on the one hand, and non-epidemic illness in the infants during the first three years. It was also found that whereas illness and/or stress had occurred in the pregnancy of 66% of mothers of the 102 retarded children, it was present in only 30% of 450 mentally normal controls, while persistent infantile ill-health occurred in 55% of the retarded, but in only 18% of controls. Moreover there were congenital malformations in 15% of the retarded sample, but in only 1.5% of the controls. To summarize, mental or physical stress on the mother during pregnancy may lead to a syndrome in the infant with three components: (1) early ill-health, including nutritional or respiratory disease, a generally ailing condition, or local infections and skin conditions; (2) mental retardation; (3) congenital malformation.

RETINAL CHANGES IN DIABETES IN CHILDREN

A German observer (*Deutsche. med. Wchnschr.*, 82: 918, 1957) draws attention once more to the high incidence of retinal changes in diabetic children. He examined with the ophthalmoscope 78 children in a summer camp and found that 17 had retinal abnormalities; five had capillary aneurysms or small capillary hæmorrhages; five had typical white exudates; eight had changes in venules. In five more children the macular reflex was absent and depigmentation was present. He advises that all diabetic children should be subjected to ophthalmoscopy every four years.

ASPIRIN IN PNEUMOCOCCAL PNEUMONIA

Workers at the Johns Hopkins University School of Medicine have shown that when pneumococcal pneumonia is treated with penicillin and hydrocortisone, there is more rapid defervescence and improvement in symptoms than in a control group given penicillin alone. Since the effects of salicylates resemble those of cortisone, a further study was made on 67 patients with pneumococcal infection of the lungs. Thirty-six received aspirin and penicillin and 31 were given a placebo and penicillin. The authors showed that although patients given aspirin appeared to improve more rapidly as regards well-being and appetite, and had less cough and pleuritic pain in the first 24 hours, there was no detectable difference between the two groups after the first day. Symptoms were abolished at the same rate in both groups. Only one patient, with chronic renal insufficiency, reacted to aspirin, but this was not a serious reaction. In 50% of these cases, the Type III pneumococcus was responsible, and this type was found in 30% of patients whose lung lesion resolved with delay. Gram-positive diplococci were found in the urine in six out of 16 cases in which the examination was made. When fever recurred it was almost always attributable to a penicillin reaction.—*Bull. Johns Hopkins Hosp.*, 101: 1, 1957.

ISONIAZID IN TUBERCULOUS MENINGITIS

Weiss and his colleagues of Philadelphia (*J.A.M.A.*, 164: 947, 1957) praise the results obtained with isoniazid in tuberculous meningitis. They have studied the case reports of 192 patients with tuberculous meningitis treated between 1943 and 1955. Before introduction of specific therapy in 1948, not one out of 42 patients survived. Subsequently when streptomycin and *p*-aminosalicyclic acid were used, the mortality rate fell to 84% in a group of 79 patients. The introduction of isoniazid in 1953 led to a dramatic further reduction in mortality to 54% in a group of 71 patients. Children under 11 years of age had a mortality rate of only 19%. The advantages of isoniazid are that it is the most potent antituberculosis agent available, that its molecule diffuses readily into the CSF, that it is effective against intracellular tubercle bacilli, that its toxicity is low, that it may be given orally if required, and that it has a definite value in preventing tuberculous meningitis during treatment of other forms of tuberculosis.

(Continued on advertising page 54)

GENERAL PRACTICE

TOXÆMIAS OF PREGNANCY: DIAGNOSIS AND MANAGEMENT*

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APPROXIMATELY one in 15 pregnant women is affected with pregnancy "toxæmia". The incidence varies from 1 to 10% depending apparently, amongst other things, on climate, geography, season, age, race, parity, diet, degree of civilization and quality of prenatal care.

The toxæmias of pregnancy remain a challenge both to the research worker and the clinician. The etiology is still unsolved, though theories abound; the treatment is still unsatisfactory and perforce empirical, though great strides have been made in recent years. Whereas in the past the great triad of maternal killers consisted of, in the order of gravity: (1) infection, (2) hæmorrhage, and (3) toxæmia, the latter has now, in most mortality series, achieved the dubious honour of first place. In addition, the toxæmias contribute a major share in the causation of spontaneous and induced premature births, and to a lesser extent, intrauterine fetal deaths.

The pregnancy toxæmias constitute a heterogeneous group of varied symptomatology, but with the single common characteristic of hypertension. Indeed, as no toxin has yet been discovered as a basic cause, the term toxæmia could be discarded and the more accurate phrase "hypertensive diseases or syndromes of pregnancy" substituted. Several gestational abnormalities such as hyperemesis, acute yellow atrophy of the liver, and ptyalism, formerly included under the toxæmias of pregnancy, are now excluded and considered as separate, unrelated, non-hypertensive entities.

The hypertensive (or toxæmic) diseases may be subdivided into two major classes:

1. *Hypertensive Disease Peculiar to Pregnancy.*

(a) Pre-eclampsia—mild, severe.

(b) Eclampsia—convulsions, or coma only.

This class comprises about 50% of all toxæmias, and is also known as the *late or true toxæmia of pregnancy.* This acute syndrome is *caused by pregnancy* and occurs in the previously normotensive woman. No counterpart is found in lower animals or in the human male. Termination of pregnancy is usually followed by return to a normal state provided the process is short-lived and appropriately treated. It is thus a *complication of pregnancy.*

The other large group of cases is known collectively as:

2. *Hypertensive Disease Not Peculiar to Pregnancy.*

This includes all hypertensive syndromes of a chronic nature antedating pregnancy. Here pregnancy is the complication of such disease and not the cause of it. The group consists of cases of: (a) *Primary* or essential hypertension, benign or malignant. (b) Essential hypertension with superimposed pre-eclampsia. (c) *Secondary* or symptomatic hypertension, due to: (1) hyperthyroidism; (2) adrenocortical hyperfunction (hyperplasia, adenoma, carcinoma).

3. *Renal Disease:*
   Bilateral (*Medical*)—(a) acute and chronic nephritis; (b) congenital cystic disease. Unilateral (or *Surgical*) – obstructive lesions.
4. *Coarctation of aorta.*
5. *Phæochromocytoma.*

Only the first group will be considered here.

Diagnosis — Pre-eclampsia occurs typically after the 24th week of gestation. Cases found before this time are usually associated with hydatidiform mole, especially if the uterus has reached the level of the navel (Acosta-Sison).[1] The syndrome is characterized by excessive retention of salt and water in the tissues, hypertension and proteinuria. The presence of any two of these three signs is considered adequate to establish the diagnosis. However, the writer is of the opinion that hypertension should invariably be present, and if either œdema or proteinuria be associated, the diagnosis may be made with confidence. Œdema and albuminuria without hypertension may occur in decompensated heart disease, in nephritis or in orthostatic proteinuria, but obviously one would not call these pre-eclamptic states.

Symptoms such as headache, vertigo, visual impairment, and epigastric pain develop only in advanced cases of pre-eclampsia, or with eclampsia imminent. Therefore, the early diagnosis depends on objective evidence and not on the patient's complaints – it is a disease of signs, not symptoms.

WATER AND SODIUM RETENTION

Water and sodium retention develops in all pregnancies, probably because of the high concentration of placental steroids which are known to promote tubular reabsorption of salt and water in the kidney. The purpose of this increased reabsorption is to produce the normal hydræmia and increased blood volume necessary for the normal progress of gestation. Extra plasma water: (1) raises the total blood volume to fill the tremendously increased vascular capacity of advancing pregnancy; (2) provides an adequate vehicle for the increased nutriment, wastes, and hormones required; (3) reduces blood viscosity and thus diminishes the tendency to rising blood pressure from augmented cardiac output (raised 25% or more); and (4) acts as a reserve fund to

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compensate for the blood loss associated with delivery. It is only in cases where the accumulation of water and electrolyte exceeds the normal level and "washes over" into extravascular compartments of the tissues that the state of pre-eclampsia threatens. Indeed, pre-eclampsia is now considered by many as an overextension of the maternal fluid, electrolyte and hæmodynamic changes characteristic of normal gestation. Nature uses the device of retaining sodium ions during pregnancy only as a means of holding back corresponding volumes of water which, as we have seen, are necessary for the needs of a rapidly changing maternal physiology.

If this intricate process gets out of balance or if excessive salt be ingested in the diet, the tissues of the gravida may be over-flooded with fluid. This will be reflected in *unduly rapid (or excessive) increments in weight* as determined by careful periodic weight measurements at prenatal examinations. Gains exceeding one pound per week after the first trimester may indicate such excessive water retention, but more often are merely due to over-ingestion of food. *Diminution of total urine output* (oliguria) will develop, step by step, with fluid retention, but in clinical practice measurement of 24-hour urine volumes is inconvenient and cumbersome. Appearance of overt œdema, especially in the hands, face and lower abdominal wall, is a third sign of significant value in detecting water retention. Transient œdema of the feet and legs is a less valuable criterion, as it occurs commonly in normal pregnancy as a result of increased venous pressure in the lower extremities in the erect posture (utero-placental shunt plus pressure of enlarging uterus) and does not therefore necessarily indicate excessive extravascular sodium and water accumulation. However, leg œdema persisting after a night of recumbency and present in the morning is significant. In summary, the most reliable sign of water retention is provided by the scales, but as already explained, the value of weight gain records is somewhat reduced by the more common cause of excess gain, viz. over-indulgence in high caloric foods with resulting obesity. Therefore, though we admit that accumulation of water and sodium in the tissues is the earliest manifestation of pre-eclampsia, nevertheless in actual practice, estimation of blood pressure is a more reliable test, even though hypertension usually succeeds rather than precedes water retention. Thus in the writer's view the sphygmomanometer is a more reliable tool than the scales in the early diagnosis of pre-eclampsia.

As the maternal tissues become "waterlogged" and thus overstocked with tissue wastes from stasis, the economy undoubtedly is forced to correct this dangerous state of affairs. Stasis of blood and tissue fluid in the rapidly growing utero-placental system may conceivably trigger the release of pressor substances which, entering the general circulation, produce generalized vasospasm with consequent hypertension. The purpose of such rise in blood pressure may be construed as a compensatory effort of nature to speed up blood flow and capillary perfusion to offset excessive water accumulation and stasis in the tissues. There are some who believe that this rise in blood pressure stems from the kidney rather than the placenta, as it has been demonstrated experimentally that diminution or occlusion of renal blood supply touches off production of a pressor substance renin, which in turn activates an angiotonin, the ultimate arteriole-constricting agent. However, if this be true, one would expect that in the male or female with congestive heart failure, hypertension should develop, as the tissues are similarly œdematous. This does not happen and consequently there must be some factor peculiar to the pregnant woman which sets off this chain of events. The pregnant woman differs biologically from her non-pregnant sister only in possessing a new circulatory and endocrine structure, the *placenta*. Thus it is that attention has been focused on this organ as the probable fons et origo, not only of all the maternal (physical and psychical) changes characteristic of normal pregnancy, but also of that peculiar pregnancy abnormality called pre-eclampsia.

The placenta is not fully formed until the 12th to 16th week of gestation, and local pressure changes due to fetal growth are of no moment, as the uterine wall grows at a faster rate than the fetus. But at the 20th week conversion of a spherical to a cylindrical uterus (elongation) occurs (Reynolds,[2] Gillespie[3]). From the 20th to the 24th week this change in conformation produces a definite but transient diminution of intra-uterine tension and hence placental pressure. However, as the uterine wall ceases to grow after conversion, the increasing growth of fetus (which is accelerated tremendously from the 20th week on) now causes uterine stretching and thinning and conceivably retards myometrial blood flow. *Thus it is possible that the combination of excess tissue water and reduced placental flow converging at or about the 20th week causes such marked circulatory stasis that the fetus is imperilled from hypoxia and the hypertensive mechanism is evoked to counteract the stagnation.* Such a mechanism if transitory could be beneficial; if prolonged the generalized vasospasm would lead to visceral ischæmic changes culminating in eclampsia (C.N.S.), abruptio (decidual vessels), fetal death, anuria (renal ischæmia), and the ultimate demise of the mother. This is another example of an initially salutary adjustment overshooting the limits of normality and eventually destroying the host herself.

Such a hypothesis would help to explain the commonly observed and accepted clinical facts:

1. Pre-eclampsia occurs mainly after the 24th week. Circulatory placental stasis is insufficient until then to evoke placental pressor substance release even with the stasis due to water-electro-

lyte retention. In hydatidiform mole in the first and second trimester and reaching to umbilical level, all the factors necessary for pre-eclampsia develop even though the 24th week has not been reached. Hence the high incidence of pre-eclampsia with hydatidiform mole, the only example of pre-eclampsia occurring early in pregnancy.

2. Multiple pregnancy carries a higher incidence of associated pre-eclampsia. The larger placenta produces more steroids, tubular reabsorption is over-stimulated, more water and salt are retained. At the same time the greater bulk of uterine contents causes earlier myometrial stretch with thinning and vascular stasis after conversion.

3. Pre-eclampsia occurs predominantly in first pregnancies. Presumably a parous uterus adjusts itself to over-stretching after conversion more successfully than the untried primigravid uterus. In addition, the vascularity of the parous uterus is probably greater and hence resists thinning from overdistension more safely, so far as free myometrial placental blood flow is concerned.

4. Pre-existing hypertension and diabetes favour development of superimposed pre-eclampsia. In these diseases arteriolar narrowing has already occurred and placental myometrial stasis will occur earlier and more readily than with a previously normal and healthy uterine vasculature.

Acosta-Sison,[1] in a recent editorial, has suggested that the high incidence of eclampsia in India, Ceylon, China and Philippines is due to the large spice and salt content of the native diets. In Tanganyika, eclampsia is unknown despite the absence of prenatal care and the low protein diet, since salt is a luxury there and is used sparingly. Acosta-Sison, however, ascribes the placental ischæmia to increased intra-abdominal pressure after the sixth month, whereas the writer's view is that it is due to myometrial thinning and vascular impairment. Otherwise the hypotheses are similar.

Treatment—Common salt, sodium chloride, is the pregnant woman's poison when ingested in excess. Strictly speaking it is the Na ion which, if taken in large amounts, upsets nature's attempt at reasonable blood (intravascular) hydration and diffusing into interstitial fluids attracts excessive water to maintain isotonicity; occult and later patent œdema results. As nearly all foods contain salt, a completely salt-free diet is next to impossible to prepare. The average daily intake of NaCl is in excess of 10 grams. Amounts of 2 g. or less will maintain homœostasis. Restriction of total food intake will automatically lessen NaCl ingestion. Salt-rich foods such as salted meats, fish, potato chips, peanuts, tinned soups, should be avoided and no extra salt added during cooking or at the table. Salt substitutes such as Diasal and Curtasal may be used for patients who are miserable on salt restriction regimens. The marked reduction in the incidence of eclampsia in war-torn or conquered countries, with the associated rationing of food or even semi-starvation, could be explained alone on the simultaneous lowering of sodium ion intake. Contrariwise, the rise in incidence following the last two wars paralleled the abolition of rationing. Normal Na ion ingestion during pregnancy leads to excess Na in blood and tissue fluids, due, of course, to the lessened excretion in the urine. For this reason it should be an invariable rule to advise a low salt diet for every pregnant woman, certainly after the first trimester is completed. It is believed that this routine would materially reduce the incidence of pre-eclampsia and eclampsia in the later months. Water intake need not be curtailed if salt is kept low, as the kidney will eliminate any excess with ease. Frequent rest periods in the recumbent position in normal pregnancy will facilitate water mobilization from tissues of the lower extremities by reducing the hydrostatic pressure in the veins. Sodium bicarbonate and other sodium-containing drugs must be proscribed in pregnancy. Phenobarbital in small repeated doses encourages the desire to rest and allays emotional anxiety. Lessened activity in turn diminishes appetite and makes it easier for the gravida to resist overeating—a desire almost universal in healthy pregnant women. Amphetamine tablets may be used from time to time in especially resistant cases with insatiable appetite. Oral Diamox (250 mg. tablet) daily, for four days at a time, has proved very useful in promoting diuresis in pre-eclampsia. (In a case handled recently, a pre-eclamptic lost 18 lb. in one week on Diamox plus rest.)

HYPERTENSION

Hypertension due to generalized arteriolar spasm is measured by the sphygmomanometer and by the ophthalmoscope. The retinal vessels very early reflect the degree of vasoconstriction. The normal arteriovenous (A/V) ratio of 2:3 becomes 1:2 or less with developing pre-eclampsia. Indentation or nicking of veins is also seen, but marked œdema, exudate, or hæmorrhage points to malignant hypertension or glomerulonephritis.

The blood pressure should remain within the accepted normal range from the beginning to the end of pregnancy. Elevation to the arbitrary limit of 140/90 mm. Hg is commonly interpreted as inchoate hypertension. However, a more accurate and flexible rule is a rise of 30 mm. Hg systolic or 15 mm. Hg diastolic above the original blood pressure readings found in early pregnancy. Hence, if at the early visits the reading is 100/60, a later rise to 130/75 would be significant, even though the level of 140/90 had not been reached. At the first visit the pressure may be elevated from excitement and nervousness. Only a persistent elevation need cause concern. In the middle trimester the blood pres-

sure often falls temporarily, some 10-20 mm. Hg in both systolic and diastolic readings. This is a mysterious variation but may be due to lessened peripheral resistance from the developing utero-placental shunt and reduced blood viscosity. In normal pregnancy too, general vasodilation, especially of the cutaneous vessels, is thought to occur in mid-trimester, and thus would favour lessened peripheral resistance. The pressure may rise in early labour from anxiety, and in the second stage from the efforts of expulsion. A transient fall due to blood loss occurs immediately post partum, but soon rises again as the uteroplacental shunt is abolished and the uterine vascular capacity is tremendously reduced by uterine retraction. These are all physiological fluctuations and are mentioned only that the unwary may not confuse them with the pathological.

Although, in a general way, the degree of hypertension parallels the severity of pre-eclampsia-eclampsia, this by no means always follows. Convulsions may occur in cases with pressures not above 140/90 and, contrariwise, many patients with very high readings recover without fits, coma or fetal death. Some 15% of women have been shown by electroencephalography to possess tracings of an epileptoid or hyperirritable character, and it has been surmised that such individuals are more susceptible to fits at the lower hypertensive levels.

If the blood pressure is found above normal in early pregnancy on at least two occasions, six to 24 hours (or more) apart in the absence of œdema, albuminuria, and all lesions causing secondary hypertension, a diagnosis of essential hypertension may be made.

If œdema and proteinuria co-exist in early pregnancy with hypertension, the diagnosis will lie between a hydatidiform mole with associated pre-eclampsia and glomerulonephritis, acute or chronic. Hypertension appearing for the *first time after the 24th week* and accompanied by either œdema or proteinuria or both, spells pre-eclampsia. If the pressure lies between 140/90 and 160/100 mm. Hg, it is classed as mild; if over 160/100, as severe pre-eclampsia. However, it is doubtful if such a distinction, based as it is on pressure levels alone, is valid. "Mild" cases are treacherous in that they may (if untreated) progress rapidly to fits and coma. Hypertension in pre-eclampsia is usually of moderate degree, seldom exceeding 210/110. Higher persistent readings suggest malignant hypertension or benign hypertension with superadded pre-eclampsia or finally nephritis.

Treatment.—Frequent periods of rest, restriction of salt, and barbiturate sedation as mentioned in the control of œdema, are of some value also in lowering elevated blood pressure. High pressure with generalized vasospasm appears to be the chief cause for deterioration, because of visceral ischæmia. If it can be lowered and maintained at reasonable levels, fits, coma, abruptio, anuria and fetal death are much less likely to supervene. For this reason, recent therapy in pre-eclampsia-eclampsia has been aimed at reduction of high pressures by the use of hypotensive drugs. Crisp and McCall,[4] and Assali *et al.*,[5] have presented papers on this new therapeutic approach, and the results of the small series therein quoted support the view that the treatment of severe pre-eclampsia and eclampsia may be revolutionized.

HYPOTENSIVE OR VASODILATOR DRUGS

Hexamethonium is an example of the ganglion-blocking group of agents for lowering blood pressure. It is administered by intramuscular injection in doses of 50 to 100 mg. and produces sudden falls in blood pressure. However, drug resistance often develops, and as pre-eclampsia has a larger humoral than nervous etiology, it has not proven of much value in obstetrics.

Spinal and *caudal anæsthesia* will reduce hypertension, but only for relatively short periods, and their use for such a purpose is not unattended with danger. General vasospasm seems to be less relieved than formerly thought, the hypotension depending largely on venous pooling, which aggravates rather than ameliorates tissue hypoxia. In addition, precipitous falls in pressure are difficult to avoid, and shock supervening in a "toxæmic" patient is hazardous. On recovery, rebound hypertension commonly occurs.

Veratrum viride is the traditional vasodepressant used by obstetricians over the years. Recently, many pure alkaloidal derivatives have been prepared from Veratrum, e.g. protoveratrine and puroverine, that can be administered orally, intramuscularly or intravenously. The chief untoward effect is bradycardia; no increase in visceral (renal, cerebral, placental) blood flow has been demonstrated. Thus the mother may be temporarily shielded from hypertension but fetal hypoxia continues unabated.

Hydralazine or Apresoline currently is the popular vasodepressor, as it acts both centrally and peripherally, and has been shown to augment renal, cerebral and probably placental blood flow. The dosage varies from 10 to 50 mg. intravenously as a single injection or by means of a drip. The object is to reduce the blood pressure to approximately 140/90 and maintain this level until delivery is effected. The untoward results are headache, tachycardia, vertigo, nausea and vomiting. These may be minimized by combining the Apresoline with a veratrum derivative such as Unitensin (5 mg.) (McCall[6]).

Those who have had a large experience in the use of the hypotensive drugs are convinced that much remains to be learned, especially as regards the dangers, dosage, and ultimate salvage rates. However, it is felt that a great new era in the control of pre-eclampsia and eclampsia may have been inaugurated by their use. The following advantages are cited.

1. In severe cases hypertension is the main immediate danger to both mother and fetus. Its quick reduction to and maintenance at lower levels obviates sudden development of coma, convulsions, anuria and fetal death. The physician is thus able to manage severe cases of pre-eclampsia with more confidence and with less fear of abrupt deterioration, and so gain valuable time to prepare for the only known definitive treatment, viz. termination of the pregnancy.

2. In mild and moderate cases of pre-eclampsia appearing from the 28th to 36th week of pregnancy, one can with reasonable safety "carry" the patient to a point when termination will be more likely to produce a viable and more mature fetus with correspondingly greater fetal survival rates.

3. Hypotensive drugs reduce or eliminate the necessity for the classical use of heavy sedation, hitherto the sheet anchor in conservative medical therapy. Sedatives reduce cerebral blood flow which augments hypoxia and favours coma and convulsions. Favourite drugs thus used by many obstetricians include morphine, Avertin, a variety of barbiturates, magnesium sulphate and paraldehyde. Their employment is still necessary but with reduced dosage and frequency when combined with hypotensive agents.

PROTEINURIA

Proteinuria or albuminuria is the least important evidence of pre-eclampsia, and usually occurs after the appearance of fluid retention and hypertension. The underlying mechanism for its appearance depends on: (1) constriction of the afferent renal arterioles, which leads to capillary anoxia with increased permeability to large molecular fractions, such as plasma albumin and globulin. These substances can thus escape into the glomerular filtrate, and as tubular reabsorption does not occur, they appear in the excreted urine. (2) The increased œdema of kidney substance compresses the renal veins and the passive congestion so developed leads to glomerular and tubular permeability to proteins (Bull[7]).

Amounts of urine protein vary from traces only up to 1 g. per 1000 c.c. Any amount over three plus or 0.5 g. daily is taken as the standard in the definition of pre-eclampsia. F. Browne[8] believed that proteinuria does not occur until hypertension levels of 160/100 are reached, but most observers doubt the validity of this statement.

Absence of albuminuria in the first 24 weeks of gestation, followed by its appearance thereafter, is very good evidence of pre-eclampsia. However, as so many other conditions may lead to proteinuria, too much stress must not be placed upon its occurrence.

Proteinuria early in pregnancy may indicate (1) chronic nephritis, (2) postural albuminuria, (3) pyelocystitis. It is not a feature of uncomplicated essential hypertension.

No specific treatment is available for controlling protein loss per se, although most clinicians feel that the measures already mentioned in the treatment of Na retention and hypertension indirectly will lessen the degree of proteinuria.

SUMMARY OF MANAGEMENT OF HYPERTENSIVE TOXÆMIA OF PREGNANCY

Prevention.—Pregnancy toxæmia probably cannot be prevented absolutely but attention to the following will reduce its incidence to a negligible figure.

1. Adequate, conscientious prenatal supervision and instruction.

2. *Diet*—(a) Limitation of total food intake in the last two trimesters. (b) High protein and vitamin, low fat-carbohydrate diet. (c) Restriction or elimination of all foods with high sodium content.

3. *Weight Control*—An optimal gain of 1 lb. per month during the first trimester, 4 lb. per month during the second trimester, and 2 lb. per month in the third trimester for a total gain of 20 lb. should be the target.

4. *Adequate Rest*—in the horizontal recumbent position frequently by day as well as at night throughout pregnancy.

5. The use of: (a) Oral diuretic drugs. (b) Anorexigenic agents (amphetamines). (c) Salt substitutes. (d) Mild sedatives. These will be especially indicated in cases of previous pregnancy with hypertension or pre-eclampsia, pregnancy with diabetes, twin pregnancy.

TREATMENT OF PRE-ECLAMPSIA

The objects of treatment are: (1) To prevent eclampsia. (2) To prevent or reduce the incidence of maternal vascular damage. (3) To secure a live infant of sufficient maturity to survive its delivery.

The first and second objectives are most readily achieved by ending the pregnancy, but in many cases this procedure will militate against the third objective. At present there is no known method of curing pre-eclampsia except by termination of the pregnancy. Medical therapy can ameliorate, control or arrest, but cannot eliminate the pre-eclamptic process, and is used only as a temporizing procedure until fetal viability is reasonably assured.

Admission to hospital of all cases of pre-eclampsia regardless of severity is the ideal procedure which, unfortunately, is not always feasible. However, the maternal mortality due to eclampsia would, by this step alone, be reduced to insignificant proportions. In hospital the following orders are commonly carried out:

1. Absolute bed rest.
2. Mild sedation with barbiturates.
3. Continuance of diet and salt restriction.
4. Use of hypotensive drugs in moderate and severe cases.

5. Record of 24-hour fluid intake and output.
6. Daily weight measurement.
7. Blood pressure measurements several times daily.
8. Urinalysis daily or every other day with recording of amount of albumin.
9. Ophthalmoscopic examination of retinal fundi.
10. Evaluation of fetal size, heart tones, position, presentation, pelvic adequacy and status of cervix ("the obstetric appraisal").
11. Special laboratory tests in selected cases or for research, e.g. blood urea nitrogen, uric acid, creatinine, CO_2-combining power, electrocardiogram, electroencephalogram.
12. Chest film, Rh group determination and full blood count are routine in all hospitalized cases.

All cases regardless of severity should receive from 24 to 48 hours of the above medical therapy before the pregnancy is terminated.

Cases that should be terminated immediately after such medication include:

(a) Severe cases with *eclampsia imminent,* i.e. sudden rise of blood pressure, marked oliguria, severe headache, epigastric pain, or amblyopia.

(b) All cases with marked and progressive hypertension, proteinuria, and œdema regardless of stage of pregnancy.

(c) All cases near, at, or beyond term.

(d) All cases that do *not* respond within 48 hours to intensive medical therapy.

(e) All cases that, after temporarily improving, begin to deteriorate.

(f) All cases with associated diabetes or pre-existing hypertension.

The only cases in which expectant conservative therapy for more than a few days is justifiable are:

1. *Mild* and *moderate pre-eclampsia* developing slowly before the 35th to 37th week of pregnancy. Here, in order to improve the probability of infant survival after delivery, one can postpone termination provided intensive medical treatment in hospital can be maintained and the response is favourable.

(2) Mild and moderate cases of pre-eclampsia after the 35th to 37th week where medical therapy has been effective in preventing aggravation or deterioration, and where surgical interruption is considered unwise for obstetrical reasons (e.g. a long uneffaced cervix, high presenting part, an unduly small fetus, etc.).

Nevertheless, it is doubtful whether a mild case should ever be carried more than four weeks, or a moderate one beyond two weeks. Termination of pregnancy in the vast majority of pre-eclampic patients is best carried out vaginally, by induction of labour. The method par excellence is artificial rupture of the membranes, preferably without, very occasionally with, adjunctive intravenous pitocin drip infusion. Abdominal delivery by Cæsarean section under local anæsthesia should be reserved for those rare cases where rapid termination is mandatory, or for less urgent cases in which some obstetrical indication for section is also present, e.g. an elderly primigravida with an unfavourable cervix, associated placenta prævia, diabetes, disproportion, history of long sterility.

Treatment of Eclampsia

I. Admit to private ward in hospital. Morphine grain ¼, or rectal Avertin, may be given prior to transportation from home.
II. Morphine grain ¼ on admission if not previously given.
III. Constant attendance of a nurse until recovery or death.
IV. Avoidance of overtreatment — excessive sedation, fluids, frequent manipulations, colon or gastric washouts, etc.
V. Avoidance of noise, bright lights and all other unnecessary extraneous stimuli.
VI. Constant awareness of onset and progress of labour, e.g.—
    1. Periodic restlessness.
    2. Lateral posture with frequent change to opposite side, slight Trendelenburg position.
    3. Side boards on bed.
    4. Tongue blade to prevent tongue laceration.
    5. Air-way and continuous oxygen by nasal tube.
    6. Pharyngeal suction when indicated.
    7. Tracheotomy where cyanosis and hypoxia are increasing despite therapy.
VII. Insertion of an indwelling Foley catheter, and checking of urine output, proteinuria, ketonuria.
VIII. Judicious use of sedative and hypotensive drugs.
    1. Intravenous hypotensive drugs for hypertension.
    2. Barbiturates intravenously for control of restlessness.
    3. Magnesium sulphate.
    20 c.c. 10% intravenously or 5-10 c.c. 50% intramuscularly, not to exceed 20-24 g. per 24 hours. Antidote—calcium gluconate 10% intravenously.
    4. Avertin per rectum.
    5. Hypertonic glucose 20% to 50% intravenously to promote nutrition and diuresis, and 10% glucose in water (500-1000 c.c.) to reduce acidosis.
IX. Termination of pregnancy not later than 48 hours after subsidence of convulsions with stabilization of patient's general condition. Postpartum collapse is common in toxæmia and may be treated with intravenous 3% NaCl (Tatum[9]). Medical therapy should be resumed after delivery of a pre-eclamptic or eclamptic patient and maintained for two to three days post partum. All patients who have had pre-eclampsia or eclampsia should receive a

careful survey of blood pressure, urine and eyegrounds on discharge from hospital, at six weeks and at six months post partum. Full recovery will permit future reproduction; marked residual hypertension and/or proteinuria will contraindicate further pregnancies, and intermediate degrees of recovery will demand extra vigilance in a subsequent pregnancy.

REFERENCES

1. ACOSTA-SISON, H.: *Obst. & Gynec.*, **9**: 233, 1957.
2. REYNOLDS, S. R. M.: Physiology of the uterus, 2nd ed., Paul B. Hoeber, Inc., New York, 1949.
3. GILLESPIE, E. C.: *Am. J. Obst. & Gynec.*, **59**: 949, 1950.
4. CRISP, W. E. AND MCCALL, M. L.: *Am. Practitioner*, **7**: 620, 1956.
5. ASSALI, N. S. *et al.*: *Obst. & Gynec.*, **9**: 132, 1957.
6. MCCALL, M. L.: *Am. Practitioner*, **7**: 620, 1956.
7. BULL, G. M., *In*: Practical obstetric problems, I. Donald, Year Book Publishers Inc., Chicago, 1955.
8. BROWNE, F. J.: Postgraduate obstetrics and gynæcology, Butterworth & Co., Ltd., London, 1950.
9. TATUM, H. J. AND MULE, J.: Quoted by McCall, Ref. 6.

Men and Books

JOHN RADCLIFFE

JOSEPH DALY, M.D., *Toronto*

AMONG THE NAMES often heard in Oxford is that of Radcliffe. A visitor is usually first made aware of it at the Radcliffe Camera, which is the favourite starting-point of sight-seeing tours because it is thought by many to be the chief architectural glory of the University. The name is found again at University College, at the Science Library and at the Infirmary. On a paving stone in St. Mary's Church, there is the somewhat awkwardly arranged inscription:

John Radcliffe
Dr. in Physick
Died Nov. 1,
1714, in the 65th
year of his age.

If the visitor is interested in academic matters, he should be able, without difficulty, to learn there is a Radcliffe Prize, and two Radcliffe Travelling Fellowships open to those in the study of medicine. There is a Radcliffe Travelling Fellowship in Astronomy also. The holder of this latter Fellowship must spend two of his four years' tenure in Oxford, and the remaining two years in Pretoria where the Radcliffe Observatory was transferred after it had been for a century and one-half an ornament of Oxford. It might be thought that the story of the man whose name is so ubiquitous would be familiar to Oxonians, yet most of these know only that he was a London physician who made a large fortune which he bequeathed to the University where he had spent many of his early years.

John Radcliffe was born in Wakefield, Yorkshire. For a long time it was thought that the date of his birth was 1650, as this is the date on his matriculation entry to Oxford and corresponds with the inscription marking his tomb in St. Mary's Church. It has recently been found, in the Parish Register of Wakefield, that 1650 was the birth year of an elder brother who died in infancy, and that John was born near the end of 1652 or early in 1653. Thus he was only in his 13th year when he entered Oxford in 1665. Matriculation at such an early age was not unusual in the days of the Stuarts; undergraduates were even younger in the days of the Tudors. The father of John was George, who married Sarah Loder of Wakefield. John was the fourth child and second son among the eight children born of this marriage. Sarah Loder's dowry, though only a small estate, became essential in the clothing and feeding of the family, for George did not prosper. Yet John Radcliffe seems never to have had as much vanity about the Loders as he did about the Radcliffes. It may be that the Loders were fewer in number, or they may have been unassuming people who made no pretence of being anything other than they were. They would probably have escaped altogether the notice of historians if they had not been related to John Radcliffe.

In Yorkshire, as in some of the other counties in the north of England, there were many families of Radcliffes. These varied in prestige and general usefulness. George was the best-known of the name in Wakefield, but he was not outstanding in his profession as an attorney. This lack of success in law had much to do with his seeking in 1647, as a reward for services to the Parliamentarians, an appointment to the Governorship of the Wakefield House of Correction. When he was dismissed from this post in 1661, he attributed his dismissal solely to Royalist prejudice notwithstanding that, during the Protectorate, he had several times been censured for inefficiency. His fellow townsmen apparently liked him because they elected him Governor of the Wakefield Grammar School as well as Warden of the Parish Church. There is nothing recorded of his occupancy of these posts to encourage the belief that his son had a rich paternal inheritance of ability. The father of George was Roger, who became Dean of Doncaster but never occupied a higher post, lay or clerical.

This family tree did not appear impressive to John Radcliffe when he had become wealthy and famous. He resolved to claim relationship with a more aristocratic family, and the Radcliffes of Dilston in Northumberland became his choice. The head of the Dilston Radcliffes was then Sir John who had been made Earl of Derwentwater by James II. Sir John refused

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to admit the validity of the claim put forward by the aspiring London physician, but other members of Sir John's family were not unwilling to accept the professed relationship as genuine, especially as it assured them hospitable entertainment on London visits. Encouraged by these gestures of friendship, which seemed to welcome him into the family circle, the physician assumed the Derwentwater coat-of-arms. The College of Heralds refused to confirm his use of this and when he died an order was issued by the Heralds that the arms were not to be displayed on any building erected from his estate. In his lifetime, Radcliffe defied the Heralds by putting the arms on his coach and on his cane. The Radcliffe Trustees also ignored the Heralds by placing the arms at any place they fancied, in University College, the Camera—the Radcliffe Science Library.

Radcliffe's early education was gained mainly at the Wakefield Grammar School. This had been founded as an independent school by Queen Elizabeth and in Radcliffe's youth its reputation was almost equal to that of Eton, Winchester or Westminster. The curriculum followed the usual course of classical training with much emphasis on Bible reading and Church attendance. Despite the rigour of this training in religion some of the pupils retained a measure of piety. Among those remaining piously faithful to the Established Church was Radcliffe, though it was sometimes said that his professed loyalty was an expression of his antipathy to Nonconformity rather than of his devout attachment to Anglicanism. His political views, which came early, were those of an unyielding Jacobite, and were not affected later by the fact that the Jacobite Stuarts were Catholics while Mary II, William III and Anne were in turn the recognized heads of the Church of England. On the classical side the Grammar School may have given Radcliffe an adequate training, although there is no record of his shining as a classicist, but his knowledge of physical science came at Oxford. He bequeathed nothing to the School. In fact, the only benefaction Wakefield had through him was a grant by the Trustees of his estate in 1801 for the new Church of St. John.

On March 23, 1665, Radcliffe entered as a batteler or exhibitioner on the Freestone Foundation at University College, Oxford. For University College this was a fortunate matriculation because Radcliffe's estate brought much to the College in the form of gifts and foundations. It was fortunate for Radcliffe also—the Master was a Yorkshireman who was a stern disciplinarian with decided views on the firm management of undergraduates from Yorkshire. Among tutors, Obadiah Walker, the Senior Tutor, had the most lasting influence on Radcliffe. In his life of 78 years, Walker suffered many vicissitudes; some of his ill fortune came from his religious views. Although he had become a Catholic he was unanimously elected Master in 1676 but, on the fall of James II in 1688, was forced to leave Oxford. For a time he was imprisoned in the Tower. His last years were spent in extreme poverty, the only relief of his wants coming from Radcliffe either in food and shelter as a guest in Radcliffe's house or as gifts of money or clothes. When Walker died in 1699, the funeral expenses in St. Pancras Church were borne by Radcliffe, who also put up a stone to Walker's memory.

During the Civil War, St. John's College, Oxford, under the presidency of Laud was practically the seat of the government of England. The university whole-heartedly supported the monarchy then, nor did it abandon its royalist sympathies when the Protector came to power. Although Cromwell treated the university with consideration—becoming its chancellor in 1650—its political influence during the Protectorate was relatively little. With the Restoration it regained much of its prestige. Charles II gave it further recognition as a haven of Royalty by taking the court there to escape the Great Plague of London in 1665. The apathy or intellectual stagnation (pervading the university during the Civil War) gave way to hopeful enthusiasm. Interest in the studies which came to be known as Natural Science was especially lively. Boyle, Sydenham, Seth Ward and Petty were then members of the university, and during the Commonwealth they had formed a Club or Society—later incorporated as the Royal Society by Charles II in 1662—which held meetings at Wadham College or at Boyle's lodgings in Merton Street. Elsewhere in the university energetic support was being given to antiquarian research, scientific experimentation and the collecting and publishing of medical manuscripts. The development of the Bodleian Library after Sheldon's bequest in 1652 had a stimulating effect on every form of intellectual activity. It is not too irreverent to suggest that Oxford at that time was in a state of curiosity bordering on eagerness.

A chronological summary of Radcliffe's life in Oxford begins with his matriculation in 1665. He took the B.A. in 1669, was elected a Fellow of Lincoln in 1670, gained his M.A. in 1672, and was admitted to the M.B. degree in 1675. For his doctorate in medicine, he had to wait seven years so that it was not until 1682, that he received his M.D. as a "Grand Compounder". The academic significance of "Compounder" was less important than the imposing title might suggest. It meant merely that the university put an extra expense on any candidate for the doctorate who had an income of £40.0.0 yearly from real property. Since Radcliffe was then in practice in Oxford, the university authorities probably knew that he was able, without hardship, to meet this extra expense. He had begun practice when a Fellow of Lincoln, so that, for a time, in addition to his professional earnings,

he had the stipend from his Fellowship as well as the privilege of living rent-free in college rooms. A quarrel with the Rector of Lincoln, Thomas Marshall, led to the resignation by Radcliffe of this Fellowship with a resultant loss of his stipend and his free living quarters. In the end the quarrel did more injury to Lincoln than it did to Radcliffe, for Lincoln received only a conditional bequest from Radcliffe's estate, while generous endowments were given to the university and to University College.

In 1680, Radcliffe moved to London. Dissatisfaction with the vista of a professional career in Oxford may have been the main reason for this change, but it has been surmised that he was influenced also by a promise of Royal patronage. The Duke of York visited Oxford in the spring of 1684, accompanied by his daughter, the princess, who became Queen Anne. She was to be married in the summer of that year to Prince George of Denmark, which meant that another royal household would be set up. When the marriage did take place, Charles II gave her a large establishment in Whitehall with Radcliffe as physician to the household—the post of Surgeon-Apothecary is the modern equivalent of that appointment. This recognition by the King brought Radcliffe to the notice of other members of the royal circle so that at one time or another his clientele included William III, Mary II, Anne and Anne's son, the Duke of Gloucester. Some of these patients were difficult to manage, notably William III and Anne who in their later years were both physically and mentally dilapidated. In the latter part of his professional life in London, Radcliffe was almost entirely out of favour at court but he seemed relatively indifferent to this loss of royal patronage. As he grew in fame he may have felt that success came to him entirely on his merits and that he need not suffer the wretchedness of those who hang on the favour of princes.

London physicians in the latter part of the 17th century acted mainly as consultants-general; practice was done by the apothecaries. When a question of operating arose, a surgeon was summoned by the physician, who also supervised any operation undertaken. When the patient first became ill, he visited or called in the apothecary, who, guided by the patient's physical and financial conditions, then repaired to the coffee-house frequented by the apothecary's favourite physician. When the physician had learned the patient's symptoms, he gave the apothecary a "bill" or prescription, which had to be written in Latin—outlining the treatment. Armed with these instructions, the apothecary secured the medicines, the purges, the clysters, the emetics, and the other components of the therapy evolved from the ingenuity of the physician. These remedies were administered by the apothecary, but, if bleeding or cupping was recommended, a phlebotomist or "cupper" was called. Unless the condition was serious or the apothecary was altogether baffled, the physician did not see the patient. The consultation fee was 10/6 (half a guinea). Abuses were inherent in such methods for there was no limit to the number of consultations: an apothecary could grow wealthy if he became a factotum of a popular physician. Conversely, an energetic apothecary could do much towards making an aspiring physician fashionable, if not famous.

There was no lack of able men among the medical contemporaries of Radcliffe. In knowledge he did not surpass all his colleagues, and was probably the inferior of some of them. A physician's political views had often much to do with his success or failure as a practitioner, for a change of government could result in the elevation of a mediocrity to a position for which nature had never intended him or art could ever fashion him. Despite changes in the political weather, it was possible for a man of forceful character or winning personality to gain a permanent eminence in his profession. Radcliffe's success seems to have been due to an imposing presence, a complete self-assurance, a sound common sense and a ready resourcefulness in difficulties. Among the political parties he had chosen the Jacobite in which he was active during all his London life—at the time of his death he was the senior member of Parliament for Buckinghamshire. He took little part or interest in medical politics, and, in fact, was twice censured by the Royal College of Physicians for failure to obey College regulations. His outspoken support of the Tories was helpful when he first came to London, nor is there evidence that his political views at any time did injury to his practice—"the Tories employed him because of his politics—the Whigs because of his professional skill." In religion he adhered to the Established Church, but his friendship with Obadiah Walker, his favour with the Duke of York (James II) and his claim of relationship with the Radcliffes of Dilston gave a basis for the accusation of a leaning to Catholicism. Until the coming of the Hanoverians, however, the Whigs were not always sure that it was either safe or prudent to attack anyone directly on the ground of religious affiliation.

Knowledge of Radcliffe's London career is neither extensive nor orderly. There are a few facts, some gossip, and a variety of anecdotes having to do with his management of members of the Royal Family. In the few years he was in London in the reigns of Charles II and James II his reputation had not reached the point where it demanded that he be called in consultation by either of these kings. With Mary II, who had the good manners usually found in the Stuarts, he was on a particularly happy professional footing. For a time he had the confidence of William III also but this relationship did not last—William, a cardiac asthmatic, drifted into alcoholism, thereby becoming an

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extremely trying problem for his physician. Radcliffe may have felt that the good-will of a drunkard—royal or otherwise—was no longer worth the irritation involved, or he may simply have given way to his feelings. He became so cynical and sarcastic in his comment and advice that he angered unforgivably the dour Dutchman. For this he was dismissed but it was rumoured that he was still consulted privately by members of the King's entourage in the frequent bouts of royal dissatisfaction with the physicians who remained as official advisers.

In his numerous quarrels with Queen Anne, Radcliffe was not blameless. It is true that the Queen's behaviour was often unpredictable and her demands unreasonable, but Radcliffe made little allowance either for her heredity or her acquired habits. She and her sister Mary had for maternal grandmother a country girl who came to London to work in a brewery. The brewer married her and, dying shortly afterward, left her his fortune. As a wealthy young widow, she married an impecunious lawyer, Edward Hyde, later the Earl of Clarendon. One of the children of this union, Ann Hyde, was the first wife of that Duke of York who succeeded to the throne as James II. As Duchess of York she became the mother of Mary II and Queen Anne and so by a strange irony this offspring of a brewer's widow is the only woman to have had as daughters two Queens of England. Mary II died young, leaving no surviving children. Thus it was Anne's inclement destiny to be the sole hope of the nation for an heir to the throne whose right of succession would be unchallengeable. At 19 years she was married to Prince George of Denmark, said by Charles II to be a nonentity, drunk or sober. Although George was dismal as a companion he was diligent as a sire: Anne had 17 children, only one of whom, the Duke of Gloucester, survived infancy. His death, of smallpox at the age of eleven, was probably hastened by the intensive bleeding and blistering employed. Radcliffe, who was called late in the illness, roundly denounced the treatment given and refused to have further connection with the case. Since he was one of the earliest antiphlebotomists, his indignation was undoubtedly genuine, but it lost nothing in acerbity because of his savage dislike of Dr. Gibbons who had supplanted Radcliffe as household physician. With the death of the Duke, there vanished all chances of a reconciliation between Anne and the physician.

Because they found no organic basis for her complaints, Anne's physicians said she had "vapours". This diagnosis would be made in more resounding terms by the psychosomatists of today. It is not difficult to have a measure of compassion for Anne. Estranged from her father because of the Revolution, wedded to a dullard, in a state of pregnancy most of her married life, and with a maternal lineage sneered at by the older aristocracy, she had few friends who might be relied on for disinterested advice. Hypochondriasis was a sort of refuge at first, but as she grew older she made no sustained effort to guard her health and increased in weight until she was almost unable to move without aid. Her teeth decayed early and toothlessness combined with obesity to make the eating of solid food a task beyond her resources. Nourishment could be taken only through a tube. There may have been acceptable reasons for the use of brandy which was then often prescribed as a food, but Anne's use of it passed into addiction. This frailty was common knowledge both in England and on the Continent. Her subjects nicknamed her "Brandy-face Nan" and Louis XIV once sought to gain her good-will by a gift of 1500 bottles of champagne and 500 bottles of Burgundy. Her reputation as an alcoholic lingered long after her death, for on one occasion there was scrawled on her statue in front of St. Paul's the doggerel:

> "And this is Good Queen Anne
> Who left us in the lurch
> With her face to the Pub
> And her . . . to the Church".

Anne died of a cerebral hæmorrhage in her 50th year—just three months before the death of Radcliffe. She is one of the few English monarchs whose death was never officially proclaimed. The explanation may have been that in the struggle to have the selection of the next monarch, neither the Whigs nor the Tories were willing to admit openly that the throne was already vacant.

Had Radcliffe been willing and able to retain the confidence of Queen Anne, he might have determined the succession by bringing back the Stuarts. His influence in the political world must have been thought important because the Whigs immediately sought to lessen it by accusing him of causing the death of the Queen. Since he did not attend her, was not asked to attend her, and was too ill himself to attend even if asked, this conduct of the Whigs would today be looked on as belonging to the realm of Gilbert and Sullivan. Yet for Radcliffe, the accusation was a serious matter. He was summoned by Parliament, and required to submit to an investigation as a "security risk". In defence of his loyalty, he enlisted or sought to enlist several members of Parliament—there is a record of his writing to the junior member of his county thanking him for a speech he made in defence of Radcliffe. The charges against Radcliffe were ultimately dropped, but the fact that these were made throws a more revealing light on the times than much that is given a place in standard textbooks of history.

When Anne died in August 1714, Radcliffe himself was in poor health. He had long been a heavy drinker and something of a gourmand, so it is not astonishing that his medical contemporaries gave apoplexy as the cause of death

—he probably had hypertensive heart disease, for he is said to have foretold his death from the condition of his pulse. Thomas Hearne made the diary entry that "John Radcliffe died on Monday, Nov. 1, 1714, leaving an estate of £140,000." The Historical Register of 1714 notes: "November 1, 1714, died John Radcliffe, M.D., member of Parliament for Buckingham, accounted the most eminent physician this England has ever produced. He was a man of good sense, sound judgment and admirable skill in his art, chiefly founded on the best mistress—Experience."

On December 3, 1714, Radcliffe was buried in St. Mary's Church, Oxford. The Master of University College argued that the burial should be in Radcliffe's old college, since St. Mary's had never before been so used. But Oxford University had never before been the sole beneficiary of an estate as vast, and tradition had to give way. Radcliffe's political views had made him such a controversial figure that it was feared there might be rioting at the funeral, but nothing marred the solemnity of the occasion; even the Latin oration of the Public Orator was listened to although it lasted one-half hour. For over 100 years the tomb remained unmarked, nor was there, in the church, any inscription to record the burial. In September, 1819, the tomb was accidentally opened in the sinking of a grave near the Radcliffe Vault and the inscription which is now on the paving-stone was found on the coffin-plate. There is as yet no monument to his memory in the Church.

Radcliffe had never married, and the only relatives for whom he felt obliged to provide were his two sisters. These were given a life interest, so that on the death of the last surviving sister the remainder of the estate went to Oxford University or to one of its Colleges. For his old College, University, he showed his particular affection by a gift of £5,000 to build a new quadrangle to contain the Master's Lodging as well as two sets of rooms for the Radcliffe Travelling Fellows. He gave his Linton property to furnish a total of seven scholarships tenable by undergraduates of University College. There was also established a Radcliffe Prize of the value of £50 to be awarded every second year by University College to any member of the university for a thesis on some branch of medical science. Among Radcliffe's assets was the advowson of the living of Heartbourne Worthy in Hampshire. It was provided in his will that preference in appointment to this living was to be given to University College with second choice to Lincoln College.

When Radcliffe was an undergraduate there was no Faculty of Medicine at Oxford. The teaching of medical students was carried on by the Regius Professor of Medicine, who was usually the head of a college. Two Linacre Scholars at Merton College and the Sedleian Professor of Natural Philosophy taught what was then regarded as the scientific basis of medicine. From the curator of the Botanic Garden the medical student received desultory instruction supplemented by the privilege of roaming at will through the garden, provided he identified himself by carrying a large herbal as a sign of professional or academic ambitions. Not more than three or four yearly took the M.D degree, so that the chief usefulness of Oxford to the medical profession was its privilege of incorporating foreigners to make them eligible for admission to Fellowship in the Royal College of Physicians.

To the ambitious graduate in medicine the small town of Oxford offered little opportunity for advancement in clinical practice, so that there was always a shortage of practitioners who were able and willing to give clinical instruction. In Radcliffe's view it was necessary to provide dignified residential quarters and an assured income if men were to be induced to accept academic positions. He seems to have been influenced also by the quaint notion of the Jesuits that a man could teach more effectively if he had some previous knowledge of what he was trying to teach. As a way of obtaining these potential professors Radcliffe provided for the setting up of two Travelling Fellowships to be tenable for ten years without forfeiture by marriage. All candidates were required to have the M.A. degree and to have completed the preliminary studies necessary to entrance on the Physic line. Clinical training was to be sought away from Oxford and at least five of the ten years were to be spent outside England. The remaining years might be spent as the candidate wished. If he chose to spend them in Oxford, he was privileged to reside in the rooms provided at University College from Radcliffe's donation. He was also given a seat at the High Table in the Dining Hall. It was allowable for a Radcliffe Fellow to hold an Ordinary College Fellowship but in that case he was debarred from using the rooms in University College. These scholarships have been in existence for some two centuries but have not been notably successful in fulfilling Radcliffe's hopes because few of the holders returned to Oxford. The Fellowships are now for two years, one of which must be spent abroad.

By Radcliffe's will the sum of £40,000 in yearly payments of £4,000 for the ten years following the death of his last surviving sister, was to be used for the building of a library in Oxford. A yearly salary of £150 was to be given to a librarian and £100 a year used for the purchase of books. Shortly before his death Radcliffe had chosen the site where the Camera now stands but after his death disputes arose among the Colleges about landlord's rights. Tenants also disputed the compensation offered—one tenant, with the Dickensian name of Juggins, began to rebuild so that he might have a higher award. Parliament at length ended these disputes by a Bill enabling the Radcliffe

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Trustees to carry out Radcliffe's plans. As developed by the Trustees the Camera became a library for scientific books and periodicals, and is today probably the oldest of its type in English-speaking countries. About a century after the completion of the Camera in 1749, it was necessary to have larger quarters, and the library was moved to the Parks Museum but retained the name of Radcliffe. Forty years later, in 1901, the Radcliffe Science Library was erected in the Parks and was extended in 1934 with the aid of a Rockefeller Grant. The university took over the Camera in 1927 as a part of the Bodleian. The Radcliffe Trustees still contribute to the upkeep of the Science Library.

The building of an infirmary was not suggested, and probably not envisaged by Radcliffe. It was largely chance that brought it into being. A money surplus in the hands of the Radcliffe Trustees in 1758 led them to cast about for a method of spending it "in a manner most consonant to the idea of the benefactors and most conducive to the good of mankind". The choice was a General Infirmary. Construction of this infirmary was begun in 1759 but it was not open for patients until St. Luke's Day in 1770—the delay being probably due to the enthusiasm of the Trustees leading them to spend beyond their current means. Thomas Rowney—who was for long an M.P. for the city of Oxford—gave the site of five acres, but the Earl of Litchfield, a St. John's man and a chancellor of the university, is regarded as the real founder. On December 1, 1770, about 1½ months after its opening, an observant well-wisher felt that he could best help the Infirmary by giving it a plot of ground for a cemetery—probably one of the most startling of all hospital benefactions. Additions have been made to this infirmary but the name Radcliffe has been retained. It is the hospital for the Medical School of the university.

About 1768 the Savilian Professor of Astronomy wrote to the Radcliffe Trustees that he could not carry out his duties without an observatory. He received an encouraging reply. The foundation stone of an observatory was laid in June 1772, on a site adjoining the Infirmary. As time went on, the Trustees appointed the Professor of Astronomy as Radcliffe Observer with the use of the Observatory. In 1839 a quarrel arose between the university and the Radcliffe Trustees with the result that the two offices were separated, and the Savilian Professor was left without an observatory until the university built the present one in the Parks. In 1929 the Trustees resolved to sell the Radcliffe Observatory and erect a new one in Pretoria where the atmosphere was more suitable for astronomy. Again the university objected on the ground that the Trustees' proposal meant a complete alienation of Radcliffe's bequest from the university. The High Court of Chancery was appealed to and its decision was against the university. Lord Nuffield bought the Observatory and its site—giving one-half of the site to the Infirmary for necessary extensions. The other half with the Observatory building went to the university for the use of the Medical School and the Nuffield Institute of Medical Research. The new Observatory in Pretoria was completed in 1948 and the Radcliffe Trustees now make an annual grant for its maintenance. Under the Chancery judgment the Trustees were to establish a Radcliffe Travelling Fellowship in Astronomy, and to pay the University £700 yearly towards his salary. The Fellow is to spend two years in Oxford and two in Pretoria.

Medical Arts Bldg.,
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MEDICAL ECONOMICS

TRANS-CANADA MEDICAL PLANS

At the Annual Meeting of the Commission of Trans-Canada Medical Plans, held in Edmonton on June 14 and 15, it was decided to undertake a marketing survey under the direction of the National Office with help from the Member Plans. Its purpose is to ascertain the potential number and make-up of so-called "national groups", that is, organizations having employees in two or more provinces whose needs for prepaid medical care involve the activities of two or more member plans. This survey should provide a clearer picture of the need and pattern of approach in the development of TCMP National Contracts.

To follow upon the morbidity code, the Commission has allocated funds for the drafting of a standard nomenclature of "Medical Services and Procedures". This nomenclature should facilitate the compilation of statistics at the national level. Under the jurisdiction of the Plan's medical directors committee, a small working committee of staff personnel of the National Office with Dr. Harding leRiche as consultant has now been set up to proceed with this project.

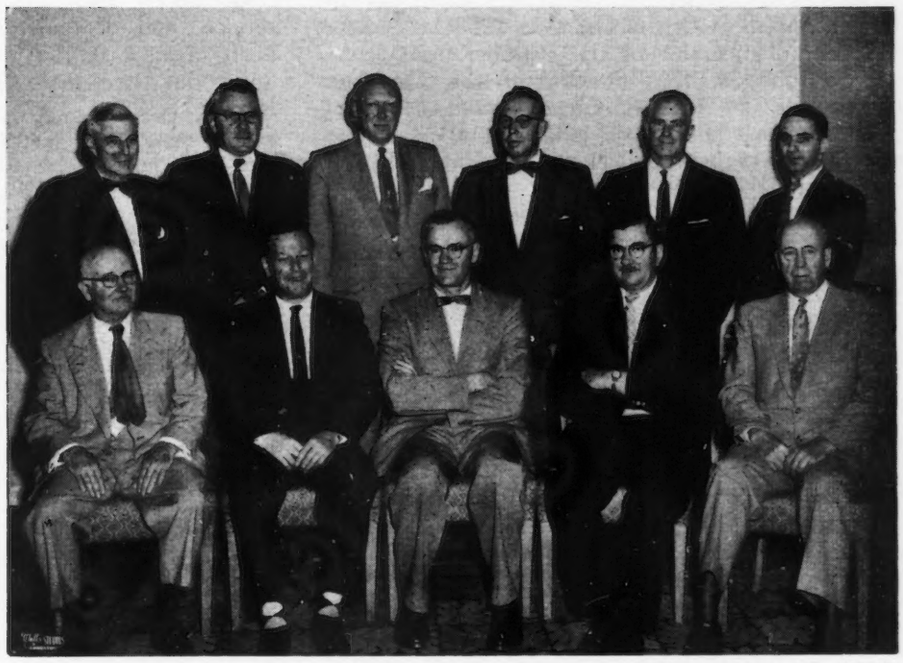
National Uniform in-Hospital Contract to be Reviewed

The executive director was authorized to review the TCMP National Uniform in-Hospital Contract with a view to possible revision of certain sections of such contracts. From the experience with the railway and other national accounts it was felt that certain arrangements had now been developed which were more satisfactory to the member plans than the pattern of rigid uniformity developed two years ago in the Uniform Contract and portrayed by the planned use of a single national "Identification Card". It was also agreed that a similar review be made of the draft for the proposed

National Comprehensive Contract and that a report on such recommendations be available for the next meeting of Plan Administrators.

Inter Plan Service Benefits

Whether or not a subscriber away from home should be entitled to the "service" benefits from the local plan where he happens to be is a point over which TCMP was unable to reach any decision. M.S.A. (B.C.) proposed "that each medical society through the medium of the member Plans, be given the opportunity to enter into a gentlemen's agreement to bring about service benefits for visitors and that this include service benefits for subscribers from Indemnity Plans when they are in a Service Plan area". This recommendation being unacceptable to many plans, it was tabled without action.



Commission of Trans-Canada Medical Plans. Front row, (left to right): Dr. H. H. Lees, Past Chairman; Dr. A. G. MacLeod; Dr. S. A. Orchard, Chairman; Dr. J. A. Ganshorn, Vice-Chairman; Dr. M. R. MacCharles, Honorary Secretary. Back row, (left to right): Dr. G. C. Ferguson; Dr. J. M. Lees; Mr. E. D. Millican; Dr. D. A. Thompson, Honorary Treasurer; Mr. George W. Wilson and Dr. E. W. Barootes.

Interplan Transfer Program.

The TCMP Interplan Transfer Program has undoubtedly been the most beneficial arrangement of any TCMP project for the public. The transfer of a subscriber's coverage from one province to another without loss of seniority is a rapidly growing service which the people of Canada fully appreciate. While it is difficult to guess at the growing size of the transfer business, orders from the national office for transfer forms have since January 1956 totalled 6000 for the TC-6 Transfer request form, and 4250 for the TC-8 confirmation form.

Joint Meeting with Executive Committee of Canadian Medical Association.

The national planning of prepaid medical care for the people of Canada is a tremendously important problem. It involves the welfare of both the public receiving the services and the medical profession providing them. It usually also concerns government who are the elected representatives of all.

In the medically sponsored prepaid programs the medical profession of Canada have set up facilities by which the majority of the people of Canada can obtain protection for themselves and their families. Such organizations require a close liaison at all times between the bodies concerned. While this fact has been well understood at the provincial level, there have been varying opinions as to how such a liaison should be best maintained nationally.

In order to debate many of these matters a joint meeting has been agreed upon between the Executive Committee of the Canadian Medical Association and the Commission of TCMP for some time in the coming autumn. Bearing in mind the successful outcome of the January 1957 conference, it is felt that such a meeting will provide much useful discussion and thought for all concerned.

Association Notes

CANADIAN COMMISSION ON HOSPITAL ACCREDITATION

Dr. William I. Taylor of Peterborough, Ont., has been appointed director of the Canadian Commission on Hospital Accreditation. Dr. Taylor is taking charge of the hospital accreditation program on September 1, succeeding Dr. K. E. Hollis. A graduate of Queen's University in 1935, Dr. Taylor served a rotating internship at Kingston General Hospital and went into general practice. In 1942 he enlisted in the Royal Canadian Army Medical Corps and served for four years.

On discharge in 1946, Dr. Taylor joined the Department of Veterans Affairs, Ottawa, occupying the positions of director, Foreign Relations;

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director, Professional Standards; and subsequently, director, Medical Organization. In 1953 he became medical administrator of the Peterborough Clinic.

Dr. Hollis, retiring director of the Canadian Commission on Hospital Accreditation, was appointed to that position on January 1, 1954. Before that, he was superintendent of Sunnybrook Hospital, Toronto.

THE LONDON LETTER

(From our own correspondent)

REFORMING THE N.H.S.

A detailed scheme for reform of the methods of financing the payment of doctors' fees and hospital charges, and provision of drugs and appliances, which, it is claimed, would effect an immediate saving to the Exchequer of around £140 million a year has just been published by the Fellowship for Freedom in Medicine, the only medical organization in this country whose aim is "to protect the public and the medical profession from State Monoply in Medicine". The basis of the scheme is state-subsidized compulsory insurance of doctors' and hospital fees by those in a position to pay for it, and a free health service for all others. All employed, self-employed and non-employed persons would be required to insure with an approved (non-profit-making) insurance society against the risk of ill health. Their contributions would cover any dependents. Pensioners and others whose income fell below a prescribed level would not be required to insure; they and their dependents would be wholly a charge on the state. All insured persons would be required to make a small at-the-time contribution to doctors' and hospital fees. Family doctors would be paid according to the service they rendered their insured patients. Drugs and appliances would be paid for on the basis of the Australian system: i.e. "vital" items would be provided free, all others being paid for in full by the patient. The financial details of the scheme show that for roughly the price of 10 cigarettes a week, the insured person would be covered (with his dependants) for about 88% of his doctor's bills and 96% of his treatment as an in-patient.

Among the advantages claimed for the scheme are that "the traditional and invaluable personal relationship between doctor and patient would be restored", the family doctor would regain his status and his enthusiasm for his work, and pressure on hospitals would be reduced by the incentive given to family doctors to diagnose and treat in the home or office many patients now referred to hospital.

RESEARCH IN ANÆSTHETICS

What is described as the only anæsthetic research department in the country which is free from the responsibility of providing a hospital anæsthesia service, and of undergraduate teaching, has just been opened at the Royal College of Surgeons, under the directorship of Dr. R. F. Woolmer. Full clinical facilities are available for the staff by arrangement with some of the London hospitals, and the department also undertakes postgraduate teaching. The initial research program covers hypothermia in experimental animals, and human respiration during anæsthesia.

A TUBERCULOSIS CENTENARY

On July 26, the Rt. Hon. Walter Elliott, High Commissioner to the Church of Scotland, unveiled a plaque on the wall of 13 Bank Street, Edinburgh, where Sir Robert Philip founded the first tuberculosis dispensary in the world in 1887. The plaque has been provided by the National Association for the Prevention of Tuberculosis to commemorate the centenary of Philip's birth. As a further commemoration, the Association has produced a small volume of "memories of his friends and pupils". This provides a fascinating picture of one of the greatest sons of the Edinburgh School of Medicine. Public memories are notoriously short, and it is only fitting that the opportunity should be taken to recall the outstanding contributions which Philip made to the understanding and conquest of tuberculosis. To many who had the privilege of studying or working under him the predominant memory is of the man himself—the autocrat who could brook no opposition but was ever loyal to his staff and considerate of his patients, the exemplar of gracious living who was mercifully called to his Maker just before the Second World War brought crumbling about our ears the remnants of that Edwardian world of which he had been such a distinguished citizen.

THE DOCTOR ON THE AIR

Much interest has been aroused by Professor L. J. Witts's frank article in the July issue of *The Practitioner* on "The Doctor on the Air and in the Press". In brief, his view is that "it would be wiser for the General Medical Council to withdraw or modify its warning against broadcasting by name and for the Ethical Committee of the British Medical Association to draw up a recommended code of behaviour, rather than that we should have an absolute ban on names which is inappropriate in so many instances". In his opinion "anonymous broadcasts are only slightly less offensive socially than anonymous letters". Nor does he accept the argument that personal broadcasting is particularly liable to undermine the confidence of patients in their family doctors. Neither is he impressed with the argument that personal broadcasts will encourage hypochondriasis. As he points out, "there are arguments against spreading information about medicine at all", and "willy nilly the public is going to get news about what is happening in medicine".

London, August, 1957. WILLIAM A. R. THOMSON

ABSTRACTS *from current literature*

MEDICINE

Amyloidosis: Clinical and Pathological Manifestations.
G. L. BERO: *Ann. Int. Med.*, 46: 931, 1957.

The nature, incidence, pathology, pathogenesis and clinical manifestations of amyloidosis are discussed, and 12 cases are presented. Of these, three were considered to be primary and nine secondary. These three cases of primary amyloid disease bring to about 100 the cases reported in the literature to date. The nine cases of secondary amyloidosis were related to arthritis in three instances, to Hodgkin's disease in two, to infections occurring in traumatic paraplegia in two, and to tuberculosis and carcinoma in one each. Nine of the patients died of amyloidosis, and three died of their underlying disease. The diagnosis was verified pathologically in all 12; in 10 complete necropsy was done. The Congo red test established the diagnosis in eight of 10 cases.

All had evidence of renal disease; five patients had renal tubular acidosis, and died of renal insufficiency. Two cases of adrenal cortical insufficiency due to amyloid disease are reported. Hepatic function was altered in all, and jaundice was present in one instance. The chemistry of the hepatic disturbance closely resembled that of obstructive hepatic disease. Involvement of the vascular tree led to thrombotic episodes in two cases and to massive hæmorrhage in three. Gastro-intestinal hæmorrhage and diarrhœa were observed as evidence of intestinal amyloidosis. Comment is made on the frequency of septicæmia, the absence of hypertension, and the nature of myocardial involvement in this disease. A suggestive relationship is noted between the appearance of amyloidosis and the use of nitrogen mustard in Hodgkin's disease

S. J. SHANE

Clinical Manifestations of Hypopotassemia.
B. SURAWICZ *et al.*: *Am. J. M. Sc.*, 233: 603, 1957.

During a seven-month study, 557 cases of hypopotassæmia were encountered in 2786 potassium determinations. The incidence among females was significantly higher than among males. The mortality of hypopotassæmic patients was strikingly higher than the over-all hospital fatality rate.

Fifty such patients were selected for detailed evaluation. Several possible causative factors for hypopotassæmia were present in nearly every case Hypochloræmic alkalosis with hypocalcæmia commonly accompanied potassium deficit. Patients with the lowest plasma potassium levels had also lowest plasma calcium and chloride levels and were more alkalotic.

Clinical abnormalities were of the type often encountered in seriously ill patients with or without hypopotassæmia. Of all clinical abnormalities, only decrease of the activity of the deep tendon reflexes showed some correlation with decrease in plasma potassium level. Rapid infusion of potassium was used as a method of suggesting which of the signs and symptoms found on initial examination might have been due to potassium deficiency. The most significant changes accompanying infusion were improved mental status and increased peristaltic activity. Further changes observed after several days of potassium repletion were difficult to evaluate, for many other therapeutic procedures also had been carried out. The nonspecific nature of the clinical manifestations of hypopotassæmia in this seriously ill, mentally beclouded group of patients emphasizes the importance of electrocardiographic and other laboratory aids in diagnosis.

S. J. SHANE

The Syndrome of Relief of Angina Pectoris Following Myocardial Infarction.
J. D. MATIS AND H. A. SOLOMON: *Dis. Chest*, 31: 622, 1957.

While it has been frequently observed that angina pectoris is experienced for the first time after an episode of myocardial infarction, it is well known that angina pectoris may be relieved following myocardial infarction. Cases are reported which illustrate relief from severe and often intractable angina pectoris following acute myocardial infarction. While the cases described showed varying clinical manifestations and varying localization of cardiac lesions, there was the common experience of relief from chest pain following acute coronary artery occlusion. In two cases, the angina pectoris became more intense after the first episode of myocardial infarction, but was relieved after the second. In a third case, the myocardial infarction afforded relief from angina pectoris which had been present for four years. There was also evidence of increased coronary reserve in that the patient was able to increase his activities greatly. However, death occurred through a new coronary thrombosis two years later, in spite of the patient's wellbeing. In another patient there was relief of chest pain after myocardial infarction. Death occurred some three years later.

Those who experienced relief of angina after myocardial infarction evidently have increased functional capacity. Whether this relationship indicates a better life-span remains to be determined. It would seem that one could draw a parallel between the cases described which indicate compensatory collateral circulation and the recently proposed surgical procedures which attempt to increase and promote circulation through revascularization of the heart.

The likely explanation for the relief is that compensatory collateral circulation had developed during the period when angina pectoris was present. In addition to the theory of increased collateral circulation following coronary artery narrowing, it has been thought that transformation of an ischæmic myocardial area into scar tissue might prevent the origin of painful stimuli. The latter theory seems less likely in view of the relatively good functional capacity after myocardial infarction in the patients described.

S. J. SHANE

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SURGERY

The Prophylactic Treatment of Malignant Disease with Nitrogen Mustard and Thio-Tepa.

G. O. MCDONALD *et al.*: *Ann. Surg.*, 145: 624, 1957.

The frequent demonstration that cancer cells may be dislodged into the blood stream, lymphatics, bowel lumen, peritoneum, etc., during operations to resect malignant lesions led to experiments using anticancer agents in a prophylactic way. Using rats, a suspension of cells of the Walker rat 256 carcino-sarcoma was injected into the portal vein and the anticancer agents were also injected. The data obtained are considered scout work for the clinician.

Both nitrogen mustard and Thio-Tepa (triethylene thiophosphoramide) were effective in decreasing the percentage of "takes". Small doses of cancer cells were not effective in producing in either the control or the treated animals. Doses twice as large were not as effectively controlled by the drugs used. Most resistance to small doses of cancer cells seems similar to that in minor contamination of wounds with bacteria.

In these experiments, the nitrogen mustard or Thio-Tepa was given on the day of the injection of cancer. In human patients, nitrogen mustard given on the day of operation increases the risk, but it has been tried on 45 patients. It may be that nitrogen mustard irrigation of the operative field before closure is a logical method.

BURNS PLEWES

Non-Penetrating Wounds of the Abdomen.

R. V. BYRNE: *A.M.A. Arch. Surg.*, 74: 786, 1957.

The author, in reviewing a series of cases, points out the usefulness of diagnostic taps in this type of injury. The diagnosis may be especially difficult in the presence of multiple associated trauma such as fractures and head injuries. In only 4 out of 82 cases in which tap was used were negative results obtained while a subsequent operation revealed hæmorrhage.

In the event of a negative tap the procedure should be repeated if the clinical condition suggests the possibility of intra-abdominal hæmorrhage. This is especially applicable to cases of delayed hæmorrhage from a ruptured spleen or liver. The four quadrant tap is advocated.

One of the discussers refers to the occasional bubbly appearance in the retroperitoneal tissues in the region of the right kidney and psoas in radiographs taken following injury to the duodenum. Reference is also made to the importance of the flat plate to determine free air, ileus, gastrectasis or shadows indicating displacement of colon due to retroperitoneal ruptures. If leukocytosis exceeds 15,000, there is a 95% chance that the patient has a lacerated liver or spleen, if the clinical picture indicates this condition.

The deceptiveness of the physical findings in children is pointed out; operation is recommended if there is any question of intra-abdominal trauma.

ALLAN M. DAVIDSON

Cancer of the Tongue.

SIR STANFORD CADE AND E. S. LEE: *Brit. J. Surg.*, 44: 28, 1957.

Since Cade's article on radium treatment of cancer of the tongue in 1927, 653 cases have been studied. During the 30 years the sex incidence has changed from one female to ten male cases in 1925 to 2 to 1 in 1951-55. This seems due to a fall in the male incidence related to the decrease in gross leukoplakia in men associated with a positive Wassermann reaction and severe oral sepsis. During the years, the incidence of skeletal and visceral metastases has increased, possibly because the control of the primary lingual lesion has eliminated sepsis, pulmonary infection and haemorrhage as a cause of death. In Great Britain today, the commonest ulcer of the tongue is cancer. Practically 99% of the tumours are squamous carcinoma.

Small incipient lesions should be excised by diathermy for biopsy. Only a few days' delay is justified for observation of antibiotic treatment. No harm has resulted from biopsy which is followed promptly by treatment. If there is real doubt regarding the diagnosis, the lesion should be considered malignant.

Cancer of the anterior two-thirds of the tongue is best treated by radium implantation, which is quick and safe and restores function. Teletherapy is favoured for posterior tumours. Excision is reserved for primary resistant or recurrent cases. Doses of about 7000 r. or rather higher in small lesions gave best results. The mortality rate in this series was 2.6% and has decreased greatly since the advent of penicillin. Conventional 200-400 kilovolt x-ray treatment proved disappointing; supervoltage (2 million volts or more) is preferred. Teleradium and more recently radiocobalt has been used, mostly for lesions inaccessible to implantation of radium.

When cervical lymph nodes were involved, block dissection was considered the treatment of choice, but this was done only if the primary lesion had been controlled and the nodes were operable. Prophylactic dissection was done in only three cases. Radiotherapy was used for cervical nodes after positive ones had been removed, when they were inoperable and when the patient was too ill or feeble for operation.

The results of treatment were poor in posterior-third tumours, but in anterior two-third cases the results were relatively satisfactory, especially in small lesions and those without metastases in lymph nodes. Five-year survival rates were higher in women (39% against 24% in men) because women report earlier for treatment.

The authors consider that the swing away from radical surgery in favour of radium techniques has been well justified.

BURNS PLEWES

THERAPEUTICS

Clinical Study of Anticoagulants in Acute Myocardial Infarction with Particular Reference to Early Heparin Therapy.

G. L. EASTMAN *et al.*: *Am. J. M. Sc.*, 233: 647, 1957.

Experiences with anticoagulant therapy in acute myocardial infarction in a general hospital from 1947 through 1955 are analyzed in retrospect. Cases were divided into three groups: untreated cases, those given dicoumarol, and those given early heparin plus dicoumarol therapy. The mortality rate was higher in untreated cases but the differences are of no significance unless the early (24-hour) deaths are counted. Patients given early heparin plus dicoumarol had a higher mortality rate than those given only dicoumarol. The difference, however, was not significant. There was a lower incidence of thromboembolic phenomena in anticoagulant-treated cases compared with those receiving no anticoagulants. Hæmorrhagic phenomena occurred in dicoumarol-treated cases four times as often as in untreated cases. In cases given heparin and dicoumarol, hæmorrhages were seven times as frequent. Superficial examination of these data, in spite of the lack of statistical confirmation, would suggest that anticoagulants are of benefit. Comparison of the severity of illness in each case group, however, suggests that untreated cases in this series were more seriously ill, and differences in death rates may conceivably be due to that factor. The apparent increase in haemorrhages and the lack of significant alterations in either mortality or incidence of thromboembolism among cases which had early addition of heparin to anticoagulant therapy make its use seem unprofitable.

S. J. SHANE

A Technique for Intrapleural Administration of Nitrogen Mustard Compounds.

L. TAYLOR: *Am. J. M. Sc.*, 233: 538, 1957.

The use of nitrogen mustard compounds locally for the suppression of pleural effusions due to metastatic malignant tumours has recently been found to be more effective than intravenous or oral therapy, and can be compared with intrapleural instillation of radioactive gold and roentgentherapy. The concentration of the cytotoxic agent has been limited, however, by the failure to remove all the pleural fluid during preliminary thoracentesis. The total single dose cannot be increased beyond fixed limits, since the drug is rapidly absorbed through the pleural surfaces and may produce bone marrow depression. In this paper, a technique is described of draining the pleural space as completely as possible with the use of a polyethylene catheter before instillation of nitrogen mustard or triethylene thiophosphoramide, thus providing a higher concentration of the drug without increasing the total dose.

The preliminary results obtained warrant a more extensive trial of this technique. S. J. SHANE

OBITUARIES

DR. SHIRLEY EBENEZER BISHOP, a general practitioner and medical health officer at Kentville, N.S., died at the Blanchard Fraser Memorial Hospital there on July 7. Dr. Bishop graduated from Queen's University, Kingston, Ont., in 1939, and during the war served overseas with the Royal Canadian Air Force. He was the son of the late Dr. B. S. Bishop.

DR. A. J. LOSIER, aged 74 years, died in Chatham, N.B., on July 12 after practising more than 50 years in this North Shore town. He was born in Tracadie, and educated at Chatham, St. Francis Xavier University and McGill University. He was an honorary life member of the C.M.A., a life member of the Canadian Legion B.E.S.L. after service in the C.A.M.C. in the first World War, and a member of the Knights of Columbus.

Dr. Losier is survived by his widow, five daughters and two sons, Dr. P. V. Losier and Dr. E. Barry Losier, both of Chatham.

DR. JAMES M. McCORMACK, 77, who had practised in Toronto for 56 years, died in St. Michael's Hospital on July 28. He graduated from Trinity College, Toronto, in 1901. Dr. McCormack was associated with St. Michael's Hospital in its early days, and was senior physician on the consulting staff in medicine.

He is survived by his widow, a son and three daughters.

DR. DOUGLAS ROBERT SHEWAN, 74, who practised in Vancouver and South Vancouver, B.C., from 1910 until his retirement in 1945, has died. He was born in Montreal, and graduated from McGill University in 1908. Dr. Shewan was a life governor of the Vancouver General Hospital. In 1949 he was given life membership of the College of Physicians and Surgeons of B.C. He was also a member of the Canadian Medical Association.

Dr. Shewan is survived by a son and a daughter.

DR. JAMES BECK SWANSTON, 78, formerly a physician at Shaunavon, Sask., died in the Mineral Springs Hospital, Banff, Alta., on July 8. He was born in Ontario, and graduated from the University of Toronto in 1906. He practised at Gull Lake, Sask., and in 1911 moved to Shaunavon, when the town had just been established. He continued to serve that district until he retired in 1945.

He is survived by his widow and three daughters.

DR. J. ARTHUR VALOIS, 49, assistant medical superintendent of Ste. Anne's Hospital at Ste. Anne de Bellevue, Que., died on July 18. He graduated from the University of Montreal in 1940.

Dr. Valois is survived by his widow.

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DR. R. A. H. MACKEEN—AN APPRECIATION

"Bob MacKeen"—a man whose name will long be remembered. His passing has removed a personality which has left its imprint on all who had the good fortune to know him well. The thought of Bob's perpetual absence from our midst leaves us with a sense of inadequacy and a feeling of incompleteness. His jovial and friendly, yet straightforward Gaelic personality made him approachable at all times when advice or help was sought. The keen mind he possessed enabled him to readily perceive the essence of any problem, and in turn aided us in reaching a solution quickly. His ever present subtle humour in both serious and superficial trends was something we always relished, because it always carried a point. It will be difficult for us to find a replacement for a man with such qualities.

In war and in peace, his influence was felt. The service he rendered his beloved country in the recent World War had far-reaching implications. As senior serologist to the Canadian Army Overseas, he developed a smooth-working establishment. This was not his sole responsibility. As a pathologist he was called upon to utilize the knowledge of his specialty in all its aspects, and in this capacity he was called as an important witness in the postwar trials in Germany.

In peace, he showed great administrative ability in the organization of the pathological and clinical laboratories in the province of New Brunswick. Starting with one laboratory in Saint John, he gradually increased the number to four in the province. Much of the success of this growth can be credited to him and his capable direction. His recognition of the needs both present and future of the department he directed kept him abreast, if not ahead of the times. The far-reaching beneficial effects of his organization to the people of this province can never be measured. Undoubtedly the concentrated planning, detailed discussions, repeated observations, and resulting increasing responsibilities had much to do with his untimely illness. Yet had he known of the consequences, his efforts would not have been lessened. The laboratories he created are a memorial to his vision and ability.

All these accomplishments make the man, but it takes much more to make a friend. Bob was a friend to everyone, with good intent, not by showering praises and glowing gifts but by his receptiveness, assurances, frankness and sincerity. His attitude was one of fairness. His word was trusted and his loyalty unquestioned. We fortunate ones are the better for having had the privilege and benefit of his association and friendship.

His passing will leave a void, not only in his family to whom we extend our sincere condolences, but also in the medical profession and all other spheres of activity in which he participated. With humility and deep sorrow, expressed in these inadequate phrases, do we say "adieu" to a brother-in-arms, a sincere colleague and a true friend. J.T.

FORTHCOMING MEETINGS

CANADA

CANADIAN SOCIETY FOR THE STUDY OF FERTILITY, Annual Meeting, London, Ontario. (Dr. Morris P. Wearing, Secretary Treasurer, 289 Dufferin Ave., London, Ont.) November 8-9, 1957.

L'ASSOCIATION DE MÉDECINE INDUSTRIELLE DE LA PROVINCE DE QUEBEC, Conjoint Annual Meeting with Section on Industrial Medicine of Ontario Medical Association, Montebello, Que. (Dr. A. H. Visser, Secretary, Suite 718 Sherbrooke Street West, Montreal 25, Que.) October 2-4, 1957.

UNITED STATES

INTERNATIONAL CONGRESS OF CLINICAL CHEMISTRY, New York, N.Y. (Dr. John G. Reinhold, 711 Maloney Building, University of Pennsylvania, Philadelphia 4, Pennsylvania.) September 9-14, 1957.

THIRD INTERNATIONAL CONGRESS OF THE INTERNATIONAL SOCIETY OF ANGIOLOGY, Atlantic City, New Jersey. (Dr. Henry Haimovici, Secretary-General, 105 E. 90th St., New York 28, N.Y.) October 18-21, 1957.

FOURTH PAN AMERICAN PHARMACEUTICAL AND BIOCHEMICAL CONGRESS, Washington, D.C. (Dr. George B. Griffinhagen, Executive Secretary of the Congress, Smithsonian Institution, Washington 24, D.C.) November 3-9, 1957.

INTERNATIONAL COLLEGE OF SURGEONS, 11th Biennial Congress, Los Angeles, California. (Dr. Karl A. Meyer, Secretary, 1516 Lake Shore Drive, Chicago 10, Illinois.) March 9-14, 1958.

OTHER COUNTRIES

SOCIETIES OF FRENCH SPEAKING GYNÆCOLOGISTS AND OBSTETRICIANS, 17th Congress, Marseilles, France. (Dr. Serment, Hôpital de la Conception, Marseilles, France.) September 9-12, 1957.

THIRD CONGRESS OF THE INTERNATIONAL UNION OF THE MEDICAL PRESS, London, England. (Dr. H. A. Clegg, British Medical Association, Tavistock House, London, W.C.1.) September 13-14, 1957.

SECOND EUROPEAN CONGRESS OF AVIATION MEDICINE, Stockholm, Sweden. (Dr. Olle Höök, Secretary General of Congress, Flygvapnet, Stockholm 80, Sweden.) September 16-19, 1957.

INTERNATIONAL SOCIETY OF ORTHOPÆDIC SURGERY AND TRAUMATOLOGY, 7th Congress, Barcelona, Spain. (Dr. J. M. Vilardell, Secretary of Congress, Avda Jose Antonio, 654, Barcelona, Spain.) September 16-21, 1957.

WORLD MEDICAL ASSOCIATION, 11th General Assembly, Istanbul, Turkey. (World Medical Association, 10 Columbus Circle, New York 19, N.Y.) September 29-October 5, 1957.

FOURTH INTER-AMERICAN CONGRESS ON BRUCELLOSIS, Lima, Peru. (Dr. Alice C. Evans, 1661 Crescent Place, N.W., Washington 9, D.C.) October 6-8, 1957.

SYMPOSIUM ON THE PUBLIC HEALTH ASPECTS OF CHRONIC DISEASES, World Health Organization, Amsterdam, Netherlands. (WHO Regional Office for Europe, Palais des Nations, Geneva, Switzerland.) September 30-October 8, 1957.

FRENCH CONGRESS OF OTOLARYNGOLOGY, Paris, France. (Administrative Secretary, French Congress of Otolaryngology, 17, Rue de Buci, Paris, France.) October 15-18, 1957.

ASSEMBLY OF ASSOCIATION OF FRENCH-SPEAKING DOCTORS, Paris, France. (General Secretary, Congrès, Français de Médecine, Prof. G. Boudin, Paris, France.) October 16-18, 1957.

CONGRESS OF THE INTERNATIONAL SOCIETY OF SURGERY, Mexico City, Mexico. (Dr. L. Dejardin, 141, rue Belliard, Brussels, Belgium.) October 27-November 2, 1957.

PROVINCIAL NEWS

BRITISH COLUMBIA

Dr. William D. Stewart of Vancouver has become the first recipient of the Maurice Husik Prize for his outstanding investigative work while a matriculate with the Department of Dermatology and Syphilology of New York University Post-Graduate Medical School. Dr. Stewart was the senior investigator and, with Dr. Victor H. Witten, co-author of the work on "The measurement of x-radiation received by the gonads during dermatologic therapeutic x-radiation techniques". The paper will appear in a future issue of the *Journal of Investigative Dermatology*. J. H. MACDERMOT

ALBERTA

Dr. Hilda McNamara has been appointed medical officer to the Peace River Health Unit. Before coming to Canada Dr. McNamara served with the Colonial service in Tanganyika. There are now 20 active health units in Alberta which serve populations varying from 20,000 to 55,000. The cities of Calgary and Edmonton have their own public health organizations and the remoter areas of the province are served by 33 provincial-municipal nurses who carry out some therapeutic as well as preventive measures. The health units are administered by local boards and the cost is split on a sixty-forty basis by the provincial government and the local authority. The establishment of a health unit consists of one medical officer; one nurse for each 6000 people in a rural area and one to each 10,000 in an urban area; one sanitary or health inspector and one stenographer-technician for each 20,000 people.

At the annual meeting of the Edmonton Academy of Medicine, the following were elected: Dr. E. B. Quehl, president; Dr. H. E. Rawlinson, first vice-president; Dr. H. L. Richard, second vice-president; Dr. R. E. Jesperson, secretary; and Dr. B. M. Wheeler, treasurer. W. B. PARSONS

MANITOBA

On July 12 some 25 friends of Dr. C. R. Rice met for dinner in the Medical Arts Club, Winnipeg, to honour him on his retirement after nearly 50 years of practice as a gynæcologist in St. Boniface and Deer Lodge hospitals.

Miss Ruth Monk will retire at an early date as librarian of the Medical Library after 35½ years' service. She has been very helpful to the doctors and students seeking information and guidance, and she has seen the library grow from its early state, housed in a few rooms in the old part of the medical college, to its present proud position in the new library building opened last year. On July 17, she was guest of honour at a gathering in this building. Dean Lennox Bell presented her with a wrist watch and President Hugh Saunderson handed her a cheque as a token of the esteem in which she is held by doctors and friends throughout the West. Miss Monk will make a leisurely trip around the world, stopping off in New Zealand and the Balearic Islands.

Manitoba Medical Service has approved the choice of carrier to provide additional group life insurance for medical members of M.M.S. The present coverage is $15,000 to age 60 years. Proposed is an additional $15,000. These amounts reduce for ages between 60 and 70 years.

ROSS MITCHELL

ONTARIO

The Hon. Mackinnon Phillips, M.D., Minister of Health, has announced the establishment of the Division of Health Information, replacing the Publicity Division of the Ontario Department of Health.

Under the direction of Kenneth L. Hawkins, the unit will endeavour to broaden the scope of general public health knowledge in the province. Mr. Hawkins was formerly Rehabilitation Officer with the Department's Tuberculosis Prevention division.

W. C. "Mac" McKenzie will be assistant director of the division, specializing in press, radio and television relations.

The resignation of Dr. L. T. Armstrong as chairman of the Medical and Surgical Advisory Committee and chief obstetrician and gynæcologist at the Toronto Western Hospital has been announced.

Dr. Armstrong had served as chairman of the medical and surgical advisory committee since July 1, 1955, and it was under his direction that the medical requirements of the hospital were developed, leading to the recent successful appeal for public support. Dr. Armstrong will continue private practice in Toronto.

Dr. R. C. Laird, chief surgeon and a member of the advisory committee, succeeds Dr. Armstrong as chairman of the Medical and Surgical Advisory Committee. Dr. R. B. Meiklejohn replaces Dr. Armstrong as head of the Department of Obstetrics and Gynæcology at the hospital.

At the same time, Dr. Armstrong resigned as an associate professor on the Faculty of Medicine at the University of Toronto and Dr. Meiklejohn has been appointed an associate professor in his place.

The Fourth Annual Clinic Day of the Niagara Falls Medical Association will be held at the Sheraton-Brock Hotel, Niagara Falls, Ontario, on Saturday, September 21, 1957.

The speakers will be: Dr. Edward Banner of the Mayo Clinic, Dr. Kenneth Alford of the University of Buffalo, and Dr. Robert Laird and Dr. Clifford Richardson of the University of Toronto.

LILLIAN A. CHASE

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QUEBEC

It is a great pleasure to record that Bishop's University in Lennoxville, Quebec, recently granted the honorary degree of Doctor of Civil Law to Dr. C. A. Peters, D.S.O., M.D.C.M., F.R.C.P., E.D., of Montreal. Dr. Peters's lengthy career since his graduation in medicine at McGill 59 years ago, and his service in the Boer and two World Wars, were cited in the presentation of the distinguished Montreal doctor

McGill University faculty of medicine recently announced a number of administrative appointments, promotions and other staff changes. Professor C. P. Leblond was named chairman of the department of anatomy. He succeeds Professor C. P. Martin, who has reached statutory retirement age. During his long term of office at McGill, Professor Martin attained the distinction of being known as one of the most proficient and thorough teachers in the faculty. McGill University has recognized this by retaining Professor Martin on the staff as part-time teacher of anatomy.

Dr. Martin Banfill has been named assistant to the dean of medicine and secretary of the faculty. He will also continue as associate professor of anatomy. Professor Donald S. Fleming gives up the post of secretary of the faculty of medicine to become full-time associate professor in the department of health and social medicine.

Dr. A. E. Moll, head of the department of psychiatry at the Montreal General Hospital, has been promoted from associate to full professor. Dr. Moll has a long distinguished academic record at McGill. He graduated in civil law in 1932 and then continued studies in the faculty of medicine to graduate in 1937. Dr. Moll joined the staff of the medical faculty in 1946.

In medicine and clinical medicine, Dr. L. Lowenstein and Dr. J. C. Beck have been promoted from assistant to associate professors, while Dr. E. M. Worden has been promoted to associate professor in pædiatrics.

Dr. Thomas Primrose and Dr. D. W. Sparling were promoted from lecturers to assistant professors of obstetrics and gynæcology.

In surgery, Dr. J. D. Palmer, Dr. G. A. Holland, Dr. Fraser N. Gurd and Dr. J. R. McCorriston have been promoted from lecturers to assistant professors.

Some five hundred delegates were present at the 23rd annual convention of the Province of Quebec Catholic Hospitals held at the Show Mart in Montreal. The convention, under the presidency of the Rev. Hector Bertrand, S.J., President of the Quebec Hospital Committee, had as its theme "The Hospital in its True Light". The convention was opened at a Pontifical High Mass in St. James' Church, sung by Msgr. Giovanni Panico, the Apostolic Delegate to Canada.

Talks and discussions covered principally questions relating to public charity patients and the cost of drugs. Approximately 20% of patients admitted to public hospitals in the Province of Quebec in 1956 were paid for by the Public Charities Act. Dr. Jean Jacques Laurier, Medical Director of St. Joseph's Hospital, Three Rivers, in discussing the professional aspects of charity cases emphasized that, in general, they receive treatment superior to that of private patients where the doctor limits the number of clinical tests and consultants in order to keep the fees at a reasonable level.

The doctor's status in the hospital, press relations and public relations in general were other themes of the convention. Sister Marie-Joseph and Sister Couture, nursing director of St. Vincent de Paul Hospital, Sherbrooke, Que., were awarded special decorations for services rendered the Hospital's Committee.

Dr. François Roy, head surgeon of Hotel Dieu in Quebec, and professor of surgery at Laval University, was elected president of the Association of Surgeons of the Province of Quebec at a recent meeting. Others elected were Dr. Léon Gérin-Lajoie, head surgeon, gynæcology department, Notre Dame Hospital, Montreal, first vice-president; Dr. C. M. G. Gardner, head surgeon of Queen Mary Veterans Hospital, second vice-president, and Dr. François Archambault of the surgical department, Notre Dame Hospital, Montreal, secretary general.

At the recent annual meeting in Quebec City, Dr. Harry L. Bacal, director of the allergy department, Montreal Children's Hospital, and lecturer in pædiatrics at McGill, was elected president of the Society of Pædiatricians of the Province of Quebec.

It is not too often that we see a McGill graduate receive a senior appointment in Toronto, but there are the exceptions. Dr. R. R. Struthers, former professor of pædiatrics at McGill and one-time physician-in-chief of the Children's Memorial Hospital (now Montreal Children's Hospital), has been named director of the Research Institute of the Hospital for Sick Children in Toronto. He will take office on January 1, 1958.

Dr. Struthers, born in Sudbury, Ontario, received his M.D.C.M. from McGill in 1918. He was for many years a member of the faculty of medicine at McGill and in 1944 was named consultant in pædiatrics to the Regional Office of UNRRA in Europe. In 1947 he was named associate director of the Rockefeller Foundation's Division of Medical Education and Public Health. He served in this position until 1955 when he returned to McGill where, under a grant from the Commonwealth Fund, he undertook a comprehensive study of medicine as taught at McGill and affiliating hospitals. Your reporter joins his many friends in wishing Dr. Struthers success and much pleasure in his new undertaking.

Your reporter would like to pay special tribute to a graduate in medicine of the University of Toronto who has attained high distinction in his

specialty at McGill and in Montreal. Dr. George Reed, who has served the Verdun Protestant Hospital for 30 years, since 1934 as the assistant superintendent and for the past 10 years as the medical superintendent, retired on June 30. Dr. Reed is a past president of the University of Toronto Alumni, Montreal branch, and of the St. James Literary Society. He was assistant professor of psychiatry at McGill and consultant to the D.V.A., the Montreal Children's Hospital and the Mental Hospital Services of the American Psychiatric Association. In the words of Dr. Heinz Lehmann, clinical director of the hospital, "Dr. Reed has brought the hospital to adulthood by knowing how to get the right people to do the right thing in the right manner at the right time. He served during the adolescence of the hospital when it acquired stature, independence, originality and individuality." Following a well-deserved rest, Dr. Reed expects to continue active practice of psychiatry in Ontario.

More than 200 persons, representing both language groups and the city hospitals, gathered one evening in June in the Windsor Hotel in Montreal to honour Dr. Harold R. Griffith on the occasion of his retirement from the posts of professor of anæsthesia and chairman of the department of anæsthesia at McGill University. A. H. NEUFELD

NEW BRUNSWICK

The Canadian Association of Pathologists, at their annual meeting at Edmonton, Alberta, elected Dr. Arnold Branch president for 1957-58. Dr. Branch is pathologist at the D.V.A. Hospital in Lancaster, New Brunswick.

The Department of Public Health of N.B. reports a number of interesting projects undertaken lately. The nutrition service sponsored a course for hospital cooks. The dental hygienist began topical application of fluoride for pre-school children in Moncton. The Health Department issued 152,800 c.c. of poliomyelitis vaccine between April 1955 and April 1957. A new tuberculosis diagnostic clinic has been opened at Dalhousie. A resident training program in psychiatry has been established in the province. A new rehabilitation centre is to be established in Fredericton in a building now being constructed. This building has been donated by Mr. Stan Cassidy.

Dr. Ralph Allanach, divisional medical officer of Victoria County, has acquired membership in the Royal Society of Health. A. S. KIRKLAND

CANADIAN ARMED SERVICES

Surg. Cdr. W. M. Little, R.C.N., has been selected to attend a postgraduate course in radiology at the U.S. National Naval Medical Center, Bethesda, Md. He has been serving on the staff of R.C.N. Hospital, Halifax, N.S.

Surg. Capt. G. W. Chapman, the Deputy Medical Director General, R.C.N., attended U.S. Atomic Energy Commission tests in Nevada in July.

Surg. Cdr. J. W. Green, R.C.N., has been selected to attend a course in anæsthesia at the Toronto General Hospital. Surgeon Commander Green is a certified anæsthetist and has been serving on the staff of R.C.N. Hospital, Esquimalt, B.C.

Surg. Lcdr. N. W. Bradford, R.C.N., who has been serving in H.M.C.S. *Bonaventure,* aircraft carrier, has been appointed to Medical Joint Training Centre, Toronto, for instructional duties.

Surg. Lcdr. C. A. West, R.C.N., who has been undergoing postgraduate training in medicine at the Toronto Military Hospital, has been appointed as Chief of Medicine, R.C.N. Hospital, Esquimalt, B.C.

Surg. Lcdr. L. M. Brown, R.C.N., who has been doing postgraduate training in anæsthesia at the Montreal College of Anæsthesia, has been appointed as anæsthetist at R.C.N. Hospital, Esquimalt, B.C.

Surg. Lt. M. Lydon, R.C.N., Squadron Medical Officer, H.M.C.S. *Algonquin,* has been appointed to the staff of R.C.N. Hospital, Cornwallis, N.S.

Surg. Lt. J. Snow, R.C.N., of R.C.N. Hospital, Halifax, has been appointed to H.M.C.S. *Algonquin* as Squadron Medical Officer.

ROYAL CANADIAN ARMY MEDICAL CORPS ANNUAL COMMAND CAMP

One of the most successful medical corps camps of recent years was held at Blackdown Park, Camp Borden, during the week of July 20 to 27. Medical units from Ottawa, Kingston, Cornwall, Toronto, Hamilton, Kitchener, Owen Sound, and London attended. In all, there were 101 officers including 30 nursing sisters, and 134 other ranks. The Formation Commander at the camp was Colonel A. S. Middlebro, E.D., of Owen Sound, who was ably assisted by his Second in Command, Lt.-Col. E. C. Armstrong, E.D., of London, Lt.-Col. G. E. Duff Wilson, of Kitchener, and other senior officers.

Qualifying courses and refresher courses were available for officers, nursing sisters and N.C.O.'s. A civil defence rescue course was also available and was conducted by Captain R. A. C. Rennie, of Central Command Staff. A vivid demonstration of rescue operations was carried out by those on the course on Thursday evening. Following a mock bombing of a demonstration building by

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the R.C.A.F., casualties simulating various injuries were rescued from different sections of a partly-demolished building. Radio commentators from CKWS, Kingston, made on-the-spot recordings of the demonstration.

The highlight of the week was a military exercise which went under the code name "Huronia" and was carried out with considerable realism under field conditions in a 40-mile area south of Collingwood. Medical troops attending the camp formed a Field Ambulance and provided medical services in support of an imaginary army brigade, which was supposedly defending the south shore of Georgian Bay from attackers from the north. Three Casualty Collecting Posts were established under canvas, using considerable camouflage against possible air attack. As the fictitious battle progressed, the C.C.P.'s were moved to other locations. The exercise was planned by Lt.-Col. G. E. Duff Wilson and directed by Colonel Wilson, Colonel Middlebro, and staff. A Field Ambulance Headquarters and Field Dressing Station combined was set up for directing the operation.

Directing staff, R.C.A.M.C. Camp. Back row, left to right: Lt.-Col. G. E. Duff Wilson, Lt.-Col. A. S. Brown, Col. A. S. Middlebro, Lt.-Col. D. B. McKee, Lt.-Col. A. Denison, Lt.-Col. G. K. McCracken. Front row, left to right: Major G. L. J. Davies, Capt. E. A. Gaviller and Capt. M. Dillon. (Lt.-Col. E. C. Armstrong was absent when the picture was taken.)

Mock casualties were evacuated over a three-day period, nursing sisters acting as casualties for part of one day. The various medical units were linked by wireless communication at all times, which was operated by the militia signal units.

Beautiful weather prevailed, with warm days and cool nights, which seemed to heighten the interest and make conditions in the Blue Mountain area almost ideal.

Air attacks by the R.C.A.F. were carried out with precision and some direct hits were scored. The bombs used consisted of small paper bags full of flour, which burst harmlessly but with surprising realism at unexpected moments, necessitating considerable attention to camouflaging of tents and vehicles.

Officers and other ranks were high in their praise of the three-day exercise which provided first-hand experience in evacuating casualties under field conditions. The scheme was made all the more pleasant by the excellent food and comforts provided for the troops. The R.C.A.S.C. School of Catering provided the regular army cooks, who used outdoor field cookers to prepare meals which would compare with the best found anywhere.

On Friday evening, a formal mess dinner was held at Blackdown for all officers in attendance. One hundred and fifty officers and guests sat down to an excellent dinner, served by Captain Sadler, Camp Catering Officer. Appropriate speeches were made by Brigadier Gordon A. Sinclair, R.C.A.M.C., and Colonel J. Magnus Spence, R.C.A.M.C., both of Toronto, and Colonel A. L. Kerr, R.C.A.M.C., of Oakville.

A ceremonial parade and march past was held on Saturday morning, and the salute was taken by Colonel A. L. Kerr, Command Medical Officer, Central Command, Oakville. Colonel Roderick Gordon, R.C.A.M.C., of Toronto, presented the "Sawbones" Trophy to Lt.-Col. A. S. Brown, Commanding Officer 26 Medical Company, Toronto, who received the trophy on behalf of his unit, for the best medical company in the Command.

Those who share the honours with Colonel Middlebro for the success of the camp are Lt.-Col. E. C. Armstrong, E.D., of London, Lt.-Col. G. E. Duff Wilson of Kitchener, and the officers commanding the various medical units, including Lt.-Col. A. G. Denison of London, Lt.-Col. G. K. McCracken of Kingston, and Major G. J. L. Davies of Cornwall. The 26 Medical Company, under command of Lt.-Col. A. S. Brown, was responsible for the administration of the camp; No. 10 Medical Company, of Ottawa, commanded by Lt.-Col. Basil Layton, was in charge of quartermastering; and the 13th Medical Company, of Owen Sound, under command of Lt.-Col. D. B. McKee, provided the transport. Officers in charge of establishing the Casualty Collecting Posts were Major G. J. L. Davies, Cornwall, Captain E. A. Gaviller, Owen Sound, and Captain M. Dillon, London.

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BOOK REVIEWS

MODERN TRENDS IN GERIATRICS. Edited by William Hobson, University of Sheffield. 422 pp. Illust. Butterworth & Co. (Canada) Ltd., Toronto, 1956. $14.50.

This is an admirable work by many authors, containing much of real value to medical practitioners concerned with the care of older persons.

The chapters on anæsthesia, gynæcology, orthopædic surgery, and chronic bronchitis are excellent detailed and accurate treatises on these subjects, but it is a pity that a section on tuberculosis in the elderly has not been included. The subject of the dermatology of senescence is especially well covered.

The weakest chapter in the book is that on glycosuria; it is a rather diffuse discussion of diabetes mellitus in general, with only casual reference to the aged, and the therapeutic advice given is not likely to be followed by many Canadian physicians. Medical therapy for the older patients is well set out, but glosses over their most difficult problem: amelioration of some of the symptoms of senility. The discussion in this chapter of cardiac atherosclerosis and its treatment is up to date and unbiased, although currently held views of the pathogenesis of atherosclerosis and coronary occlusion may require substitution in the next edition by the exact reverse of what is said here. Writing on nutritional problems of the aged the authors are somewhat verbose; for example, it requires some two pages to decide that there is an increase in body fat relative to total weight in older people. The omission of a thorough discussion of expedient methods in the home environment detracts from an otherwise admirable section on physical medicine; the author is wise in his insistence that teamwork is necessary in the treatment of the aged.

The first and last chapters of the volume on general principles suffer from opinionated statements unsupported by experimental evidence, but they are well worth reading for the valuable statistical data they contain. The chapters on hospital and home care are addressed directly to the British practitioner and bear little relevance to conditions in other countries. There is paucity of data available on biological aging and normal values, but the authors have compiled an interesting review on these and on psychological aspects of illness in the aged; the latter section unfortunately omits much North American work on the subject.

PRINCIPLES OF SURGICAL PHYSIOLOGY. Harry A. Davis, College of Medical Evangelists, Los Angeles Division. 841 pp. Illust. Paul B. Hoeber, Inc., New York, 1957. $20.00.

Most surgeons agree that there is difficulty in keeping abreast of knowledge in physiology. Surgical journals generally cover the latest advances in surgical techniques, pathology, and biochemistry, but physiology tends to be relegated to special journals of restricted circulation. This volume is a direct attempt to correct this deficiency. The author has not hesitated to enlist the help of well-known authorities in their own fields. The book is divided into general principles (covering some 240 pages) and systemic physiology.

The sections dealing with water and electrolyte metabolism and acid-base balance are worthy of special mention. In 66 pages, well illustrated with bold type diagrams, this difficult subject is covered in a clear, forthright manner. Similarly, those on oxygen and carbon dioxide metabolism and anoxia are written with a thought always to the practical aspects as they are encountered by the surgeon or anæsthetist. The chapter on nutrition in the surgical patient is novel, incorporating much of the modern writing and thought on this subject. It is divided into orderly sections, so that one can find the answer to a particular problem and pick out the "meat" without wading through superfluous material.

Another chapter deals with physiology of tissue transplants and normal and neoplastic growth: this is of immense concern to all surgeons today and is well done. Fewer than five pages are devoted to the physiology of the thyroid gland. In view of the wide interest in this field, especially since the advent of radioactive iodine, the reviewer feels that more space should have been allotted to this subject. Tests with radioactive iodine are confined to one small paragraph.

On the whole, however, this book marks a real advance in presenting physiology to the surgeon. It should prove of value to the advanced student or the busy surgeon who wants the important facts divorced from a maze of theory and experimental work behind them. This book should have a wide acceptance.

DER HIRNABSZESS (Brain Tumour). Gerhard Weber, Zürich. 188 pp. Illust. Georg Thieme Company, Stuttgart, W. Germany; Intercontinental Medical Book Corp., New York, 1957. $7.10.

This monograph on pyogenic intracranial conditions comes from the neurosurgical clinic in Zürich and is based principally on an evaluation of all cases seen there between the years 1938 and 1955. It is divided into two parts, the first on general pathology and etiology of intracranial suppuration, both of traumatic and of non-traumatic origin, and a much larger part on the symptomatology and therapy of intracranial suppuration. In the latter section are considered osteomyelitis of the skull, pachymeningitis externa and extradural abscess, thrombosis of sinuses and veins, subdural infection, purulent meningitis, and brain abscess. The last two pages of the book contain a summary of the principles of management of brain abscess and its differential diagnosis.There are many case histories in the text, and there is a very adequate bibliography at the end. The world literature finds adequate discussion and the monograph is well presented.

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VOLUNTARY HEALTH INSURANCE IN TWO CITIES. A Survey of Subscriber-Households. O. W. Anderson, Research Director, Health Information Foundation, and the staff of the National Opinion Research Center. 145 pp. Harvard University Press, Cambridge, Mass.; S. J. Reginald Saunders and Company Limited, Toronto, 1957. $6.50.

The data upon which this study is based were obtained during 1953 by the staff of the National Opinion Research Center, University of Chicago, by interviews with subscriber families in Birmingham, Ala., and Boston, Mass. Three groups are exhaustively analyzed: families covered by Blue Cross–Blue Shield in Birmingham and Boston, and by the Aetna Life Insurance Company in Boston.

The extent of coverage provided to each of the groups is comparable and consists of hospital care insurance and in-hospital physicians' services. Indemnity benefits are provided under the commercial contract and a mixture of service benefits with financial limitations and cash allowances, under the B.C./B.S. contracts.

Recognizing that the pattern of health insurance as it has developed in the United States places first priority on coverage for hospital care and surgery, this study undertakes to assess how adequate is the financial protection afforded. The answer is, not very adequate because when measured against the average total charges for *all* personal health services the insurance agencies covered only 20, 27 and 31% respectively. Subscribers were given the opportunity of expressing themselves on their desire to insure for more comprehensive cover and their willingness to pay for it. The tables on these questions are equivocal in that one indicates that subscribers of the order of 50-65% desired cover for the small medical expense while another table shows that only 3% of dissatisfied subscribers have indicated a desire for a policy covering all health expense. The willingness of subscribers to pay more varied considerably both as to its existence and in the amount.

These findings are at variance with the experience in Canada, where comprehensive medical and hospital cover on a service basis appears to be in demand and this demand is accompanied by a willingness to pay increased premiums to obtain it.

Dr. Odin Anderson will be recalled by Canadian friends as a former instructor in medical economics at the University of Western Ontario. This book reflects his scholarship and objectivity and is a valuable contribution to the literature of voluntary health insurance.

FUNDAMENTALS OF CLINICAL NEUROPHYSIOLOGY. Paul O. Chatfield. 392 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $9.25.

This volume is intended for medical students and persons seeking an introduction to neurophysiology. Although it uses the adjective "clinical" in its title, it is oriented from the neurophysiological point of view: it will not be used to solve clinical problems but rather will provide the background necessary to understand the clinical conditions. It incorporates sufficient of the fundamental physics, anatomy, and biochemistry to provide an adequate background for the neurophysiological problems discussed, but it assumes a working knowledge of these subjects.

Almost a third of the volume is occupied with a discussion of fundamental neurophysiology of the neurone and the synapse. The remainder is devoted to the organized activity of the central nervous system.

On the whole, the selection of the material is good and the space allotted to the various portions of the subject appropriate. Much of the material from recently published papers has been included: the author has sifted this and has succeeded in placing the new observations in their proper perspective. However, he has not forgotten that a knowledge of the classical papers is essential for the beginner in this field. It will prove a satisfactory textbook of neurophysiology for medical students and will find a place among the regularly used texts; it will also be of value to the practising neurologist or neurosurgeon who wants to review the subject.

ATLAS DER GASTROENTEROLOGISCHEN CYTODIAGNOSTIK (Atlas of Gastroenterological Cytodiagnosis). N. Henning and S. Witte, Erlangen; R. O. K. Schade, University of Durham, English translation. 103 pp. Illust. Georg Thieme Company, Stuttgart, W. Germany; Intercontinental Medical Book Corp., New York, 1957. $9.05.

This essay and atlas of gastroenterological cytodiagnosis has been prepared in the University of Erlangen, Germany, and the text has been translated by Dr. Schade, a pathologist in the United Kingdom.

The first section of the book consists of an essay on the cellular morphology of the gastro-intestinal tract from oral cavity to rectum and the diagnostic importance of the cells found. This is followed by a note on the collection of material and methods of examination. The whole of the text is presented both in German and in English. The second and larger section of the book consists of black-and-white pictures of the cytology of the gastro-intestinal tract, both in normal and abnormal conditions, as shown by photomicrographs of specimens stained by regular methods or examined by phase contrast. Here again the legends to the photographs are in both German and English. For study of the œsophagus and stomach, the authors emphasize their success with use of their own special tube with a foam rubber "cell swab". They draw attention to the differential diagnosis of tumour cells by intravital fluorescent staining with atabrine and fluorescence microscopy, and to the detailed examination of bile sediment which may contain degenerated liver cells or tumour cells.

The atlas is well reproduced and the whole work will be valuable to anyone interested in this new diagnostic field.

MEDICAL NEWS *in brief*

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ASIAN INFLUENZA IN U.S.A.

Surgeon General Leroy E. Burney of the U.S. Public Health Service has announced that first supplies of a U.S. vaccine against Asian influenza are expected to become available to the public during September.

Dr. Burney said the six manufacturers licensed to produce influenza vaccine have set a production goal of at least 60 million c.c. (doses) by February 1. This involves hiring additional personnel and operating two or three shifts, seven days a week.

The Public Health Service will undertake a vigorous campaign to urge maximum public use of the vaccine just as rapidly as supplies become available. The American Medical Association and the State and Territorial Health Officers will join in this effort. It is quite possible, if not probable, that even with maximum use of the vaccine the U.S.A. may have serious influenza epidemics in the fall or winter.

The Public Health Service, the American Medical Association, and the State and Territorial Health Officers are planning a co-operative public information and education campaign on the nature of the disease and steps to be taken in an epidemic.

The American Medical Association, working closely with the Public Health Service, has developed a stand-by plan for the best use of available health and medical manpower in an influenza emergency.

There have been local outbreaks in the United States this summer which normally is a season of low influenza incidence. Several thousand cases have been reported to date to the Public Health Service. Because of the nature of the disease—its swift onset and short duration—precise reports on incidence are difficult to obtain. Other respiratory infections occur which are virtually indistinguishable from influenza except by laboratory tests. Most areas of the U.S.A. have probably been exposed to the virus by now, and past experience suggests that the disease may suddenly begin to spread quite rapidly sometime in the fall or up through late winter.

Cases of Asian influenza so far have been marked by temperatures of 102 to 104° F., headache, sore throat, cough and muscle aches. The fever lasts three to five days, and is followed by weakness for several more days. The attack rate in the Far East was approximately 20%, with a death rate of about 0.2%.

Early in the Far East epidemic the Asian influenza virus was isolated by U.S. Army medical teams and shipped to the U.S.A. for analysis. On May 22, the Public Health Service sent prototype strains to licensed influenza vaccine manufacturers and work was begun immediately on the development of a vaccine against the new strain.

The Public Health Service continues to keep its epidemic intelligence services focused on influenza developments in the U.S.A. and throughout the world, with particular attention to any indication of changing patterns in the severity or incidence of the disease. Clinical agents needed for diagnosis of Asian influenza are being

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produced and distributed, and Public Health Service laboratories are investigating acute respiratory diseases. In addition, the Service is testing and evaluating the vaccine.

CONFERENCE ON PULMONARY CIRCULATION

The Chicago Heart Association will sponsor a conference on the pulmonary circulation, to be held Thursday, Friday and Saturday, March 20 to 22, 1958, at the Palmer House, Chicago. The objective of the conference is to bring together major contributors to this controversial field. Each participant will present his own work and opportunity will be provided for discussion. The meeting will be open to physicians and scientists. Introductory sessions will be devoted to the physiology, anatomy and pathology of the pulmonary circulation with special emphasis on methods of clinical study. Later sessions will cover the pulmonary circulation in congenital heart disease, primary lung disease and in acquired heart disease.

Among the distinguished visitors who are accepting major responsibility in the planning and execution of the conference are Dr. Julius Comroe, University of Pennsylvania Graduate School of Medicine; Dr. Howard Burchell and Dr. Jesse Edwards of the Mayo Clinic, Rochester, Minnesota; Dr. Paul Wood from the Institute of Cardiology, London; and Dr. Lars Werko of the University of Gothenburg, Sweden.

Further information from: Dr. Wright Adams, Chairman, Symposium Planning Committee, Chicago Heart Association, 69 West Washington St., Chicago 2, Ill.

SOME HIGHLIGHTS FROM THE LATEST REPORT OF THE MEDICAL RESEARCH COUNCIL

Some of the accomplishments realized by organizations connected with this body during the last year are briefly reviewed here.

When it was decided to replace the Mahoney strain of poliomyelitis virus by the less virulent strain Brunenders for use in Britain, new ways had to be devised for testing vaccine for safety. The inoculation of monkey kidney cell cultures did not have to be altered as these cells are equally sensitive to both strains. However, as the Indian Rhesus monkey regardless of its conditioning is insensitive to the Brunenders strain, Philippine cynomolgus monkeys had to be used instead and proved to be entirely adequate replacement. It was also found that production of antibodies in human children reached a level comparable to that obtained with the American vaccine.

Professor G. W. A. Dick and his associates inoculated strains of live but attenuated viruses directly into the brains of monkeys and found that no paralysis resulted. These attenuated strains were fed to human volunteers with no untoward reaction. It was also given to a number of babies and small children without any ill effect.

In this vaccinated series of volunteers antibodies to the type 2 strain were not found in as high a proportion as were the antibodies to the other types. As this type 2 strain is not entirely stable after injection, and thus may revert to

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NOW AVAILABLE: MYSTECLIN-V

Squibb tetracycline phosphate complex and nystatin [Mycostatin]

PEDIATRIC DROPS AND SUSPENSION

The new phosphate complex of tetracycline...

... for faster and higher initial tetracycline blood levels*

PEDIATRIC DROPS

Contains tetracycline phosphate complex equivalent to 100 mg. tetracycline HCl. and 100,000 units of Mycostatin per cc. Bottles of 10 cc. with calibrated dropper.

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Each 5 cc. teaspoonful contains tetracycline phosphate complex equivalent to 125 mg. of tetracycline HCl. and 125,000 units of Mycostatin. Bottles of 30 and 60 cc.

*Plus added protection against monilial superinfection

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Each Mysteclin-V capsule supplies tetracycline phosphate complex equivalent to 250 mg. of tetracycline hydrochloride, and 250,000 units of Mycostatin. Bottles of 12 and 100.

SQUIBB

'MYSTECLIN-V' IS A TRADEMARK

MEDICAL NEWS *in brief*

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its virulent form, further attenuation will be required before its use becomes practical.

In evaluating the degree of immunity to whooping-cough offered by vaccination, field trials were undertaken and 30,000 children between the ages of six months and three years were inoculated. Wide variations in protective activity from one type of vaccine to the other was noticed. Whereas the poorest vaccines gave an attack rate of almost 90% of that which would be expected in a group receiving no vaccine, others gave a rate of only 4 to 30% of the expected rate. The mouse protection test was also used, and confirmed the variability in immunity which had already been observed in field trials. Some correlation was demonstrated between the activity of the vaccines in the laboratory and their protective property in children.

New attempts have been made to determine as exactly as possible the required daily intake of protein. The figure of 0.35 g. of good quality protein per kilogram of body weight was found to provide a safe allowance of essential amino acids. It has been noted that patients who are in negative nitrogen balance will regain nitrogen equilibrium less effectively with a soya bean diet than with milk. A protein mixture prepared from ground nuts and Bengal grain is used for that purpose in South India. Means of detection of protein malnutrition include an evaluation of blood enzymes which may show changes in the early phase of this deficiency, and also evaluation of bone age and skeletal development which may also be influenced in such circumstances. An increase in intracellular water may mask a decrease in tissue solids. All these determinations are technically difficult and of impractical application.

A very promising tool in the investigation of protein metabolism is the advent of radioactive substances. Dr. Garrow and Mr. A. E. Piper have designed a counter for measuring radioactive sulfur in 1 mg. of protein. Dr. J. F. Done and Dr. P. R. Payne are using tritium as a tracer for similar purposes.

In the field of growth and renal function, it has been found that the kidney of the newborn is relatively unresponsive to the antidiuretic hormone of the posterior pituitary. In some premature individuals the kidney may be unable to vary the volume of urine for several weeks regardless of the needs of the body. This property of the young kidney helps to explain some apparent inconsistencies already reported, such as the presence of a very high level of blood urea with a histologically normal organ.

Dr. M. F. Prutz has shown that hæmoglobin A and hæmoglobin S have the same molecular weight, the same hæmprosthetic groups and nearly the same amino acid composition, and besides, they have the same crystal forms except when prepared by one particular method. No difference in x-ray diffraction pattern can be detected between the two. Dr. V. M. Ingram pointed out the variation in chemical composition which resides in the different position of one of 30 different peptide groups common to both. It was also shown that the glutamic

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acid in normal hæmoglobin is replaced by valine in sickle cell hæmoglobin. With loss of oxygen the S hæmoglobin molecules alter their shapes from that of an ellipse to that of a long fibril which when orientated in a parallel disposition gives the drepanocyte its peculiar shape. Allison has suggested that carriers of the sickle cell trait possess some resistance to infection with *Plasmodium falciparum* which gives them a notable advantage in survival, particularly in certain parts of Africa. It is now possible to determine accurately the proportion of fetal hæmoglobin present in the red cells of patients with thalassæmia and other hæmolytic diseases by means of a method devised by Dr. J. H. Beavan and Dr. J. C. White.

The mechanism of transduction is now being used in bacterial genetics. This process is based on incorporation through a virus of low virulence of some fragments of chromosome from one bacterium into another. Dr. M. Demerec has applied this method to the study of *Salmonella typhimurium* and Dr. B. A. D. Stocker has used it for observing bacterial motility. The process of conjugation has been studied by Dr. W. Hayes and consists of the temporary fusion of two cells during which part of the donor chromosome is transferred to the recipient cell.

Drs. Mitchison, Barnes and Loutit confirmed previous findings relative to the survival of irradiated mice into which normal blood-forming tissue had been transplanted. Following upon this experiment, the same group of workers found that normal mice to which foreign tissue had been transferred became actively immunized against tissue from the strain of mice which had supplied the original transfer. This immunization applied to attempts at implanting tumour tissue. It seems, therefore, that irradiation must have conditioned the tissues in such a way that they do not reject transferred cells any longer, as they otherwise would normally. This discovery may be applicable to patients suffering from leukæmia as it has already been shown that leukæmic mice subjected to irradiation in dosages of 1500 r. over a period of 24 hours will lose all their leukæmic cells; these animals would normally die from such exposure but are now made to survive by means of transfusion of bone marrow.

Drs. A. Stewart and J. Webb carried out a survey of children certified to have died of malignant disease in England during the period 1953-55. These investigators found out that the mothers of the latter had been subjected to x-ray examination of the abdomen during their pregnancy to a greater extent than the mothers of a control group of children. Similarly, Drs. W. M. Court-Brown and J. D. Abbatt studied a group of 9364 patients suffering from ankylosing spondylitis for which they had been subjected to radiotherapy. The incidence of leukæmia in this group was between five and ten times the expected rate as compared with other patients suffering from the same disease and not treated with x-rays.

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More work has been done by Sanger on the molecular structure of proteins in general and insulin in particular. Ox insulin contains 51 amino acids; its molecular weight is 5734. Professor W. S. Peart and Dr. D. F. Elliott applying similar technique purified hypertensin which is concerned with renal hypertension. New advance in the biosynthesis of penicillin has been achieved by Dr. H. R. V. Arnstein, Dr. P. T. Grant and Miss M. E. Clubb. By means of a stable isotope of nitrogen and radioactive sulfur, these workers were able to show that the lævo-form of cysteine was incorporated as a unit into the penicillin molecule, but that the dextro-form was hardly used at all. It appears that cysteine also plays an important part in the biosynthesis of bacitracin and micrococcin.

The mass spectrometer specifically designed for respiratory investigation and whose use was suggested by Professor J. McMichael and Mr. D. K. Hill in 1950 has finally been completed. This apparatus will greatly facilitate gas analysis in pulmonary function and should give new impetus to this branch of physiology and medicine.

THIRD INTERNATIONAL CONGRESS OF ALLERGOLOGY

The Third International Congress of Allergology will be held in Paris at the New Medical School on October 19 to 26, 1958. The scientific program will include symposia on: asthma and emphysema; physico-chemical properties of allergic antibodies; biochemical aspects in hypersensitivity; recent advances in etiology and treatment of allergic conditions; auto-immune processes in allergy; allergic management and problems in different parts of the world. In addition there will be scientific papers on immunology, histamine and chemical mediators, tests and standardization, respiratory allergy, allergic dermatitis, and therapeutics. The main papers will be translated simultaneously in English, French, German and Spanish. Information concerning the Congress is available from: The Secretary, B. N. Halpern, 197 Bd. St. Germain. Paris, 7e, France.

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ACADEMY OF PSYCHOSOMATIC MEDICINE

The program of the fourth annual meeting of The Academy of Psychosomatic Medicine to be held October 17-19, 1957, at the Morrison Hotel in Chicago will be devoted to "Psychosomatic Aspects of Obstetrics, Gynecology, Endocrinology and Diseases of Metabolism". The meeting will be open to all scientific disciplines, as well as psychologists, social workers and nurses. Information may be obtained from Dr. William S. Kroger, Secretary, 104 South Michigan Avenue, Chicago 3, Illinois.

DIET AND CORONARY THROMBOSIS

In a recent article on diet and coronary thrombosis (*Lancet* 2: 155, 1957) Yudkin of London writes, "As more and more of these awkward facts [purporting to relate coronary disease and diet] turn up, one begins to have the uneasy feeling that both the proponents and the opponents have a dietary hypothesis of quoting only those data which support their views." Indeed the curves obtained in plotting mortality from coronary thrombosis on one hand and total fat ingested per day, or calories from fat, or the proportion of animal fat compared to butter fat or vegetable fat, margarine, animal protein, total protein, sugar or total calories, fail to show any correlation which would point out one or more of these factors as the etiological agent concerned. One does not fare any better in adopting the Registrar General's classification of five classes, namely, unskilled, semi-skilled, skilled, intermediate and professional as applied to the population at large. The final blow to these comparisons is dealt by an *ab absurdo* demonstration that the best correlation is obtained when deaths from coronary thrombosis are compared over the years with the number of radio and television licences issued in the United Kingdom.

Part of the inconsistency of these dietary studies may rest on lack of information on one essential factor, which is the uniformity of distribution of foodstuff in the population studied, *i.e.* the proportion of the population to which the average standard of nutrition applies. Most of these comparisons are established on a year-to-year basis comparing the nutritional data of one particular year with the mortality rate from coronary thrombosis in the same year. One would expect that whatever influence diet may have in this respect would not become apparent for several years. However, one must keep in mind the decrease in incidence of coronary thrombosis both in England and even more so in Norway during the war years when the dietary habits of these countries were deeply modified. Even though diet may enter into play, there are probably a great many more factors which are just as important and which have been overlooked so far. The author suggests decreased physical activity as being one of them. Although the problem may seem well nigh insuperable, comparison of the diets of patients dead from coronary disease with the diets of the rest of the population might single out some factors otherwise lost in the surveys of much wider groups which are generally reported.

CANADIAN CANCER SOCIETY: ALLAN BLAIR MEMORIAL FELLOWSHIPS

Applicants for these Fellowships must be graduates in medicine of an approved Faculty of Medicine and (a) shall have had, after receipt of their degree, not less than three years of postgraduate study, of which at least two shall have been in a field related to the diagnosis and/or treatment of cancer; (b) shall under this Fellowship pursue a program of two years' further postgraduate study of the diagnosis and/or treatment of cancer acceptable to the Advisory Committee on Fellowships of the Canadian Cancer Society; and (c) shall express a firm interest and assume the moral obligation to practise his/her profession subsequently in Canada with a particular interest in cancer.

One Fellowship shall be awarded annually. A Fellowship is tenable for two years and has a value of $4000 per annum for single

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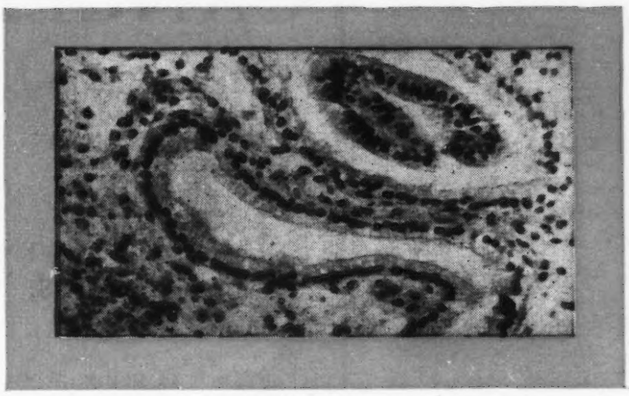
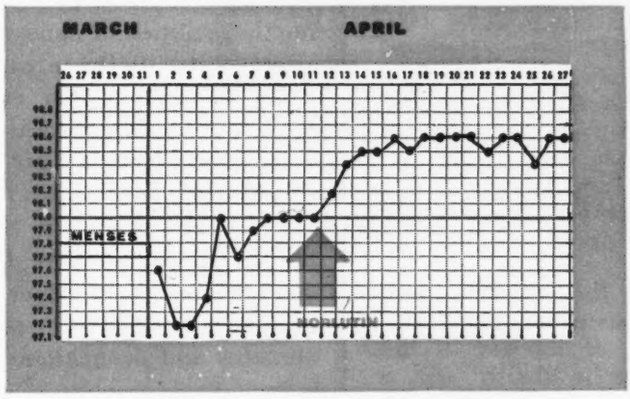
UNSURPASSED EFFICACY

in disorders of menstruation and pregnancy

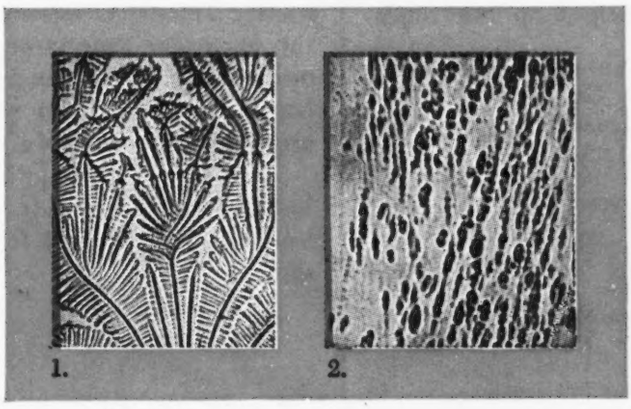


NORLUTIN: Progestational Effect on Endometrium"...10 mg. [NORLUTIN] given twice daily represents a reproducibly effective dose in women for the production of marked progestational changes in the endometrium."[3]

Presecretory to secretory endometrium after 5 days treatment.



NORLUTIN: Thermogenic Effect "This preparation was found to have a marked thermogenic, and other physiologic effects in comparatively small dosage."[4]



NORLUTIN: Abolition of Arborization in Cervical Mucus NORLUTIN "...inhibits the fern leaf pattern in cervical mucus."[5]

1. Fern leaf pattern. 2. Arborization completely abolished by NORLUTIN.

NORLUTIN: Induction of Withdrawal Bleeding "As little as 50 mg. of [NORLUTIN] administered in divided doses over a five-day period was sufficient to induce withdrawal bleeding."[2]

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Fellows and $4500 per annum for married Fellows.

Application forms may be obtained from the Canadian Cancer Society, 800 Bay Street, Toronto 5, Ont. Applications should be submitted to the above address not later than October 1, 1957. The Award will be announced November 15, 1957, and the Fellowship will become tenable July 1, 1958.

AMERICAN FRACTURE ASSOCIATION

The 18th annual meeting of the American Fracture Association, to be held at El Paso, Texas, on September 30 and October 1-2, 1957, will be preceded and coordinated with the program of the University of Texas Postgraduate School of Medicine, El Paso Division.

The program of the Fracture Association meeting will be confined to fractures, and is approved Category II by the American Academy of General Practice. The Postgraduate School program—approved Category I—will be on orthopædic surgery, and will be given on September 29, at the El Paso Medical Society (Turner) Home.

Apart from the scientific programs and discussions, numerous trips to areas of interest in the region will be available, and a representative of the Chamber of Commerce will be at the registration desk to help those who may be interested.

A postgraduate trip to the Medical University, Guadalajara, Mexico, will be planned after the American Fracture Association meeting, under the direction of Dr. Duncan McKeever.

Information can be obtained from: Dr. W. Compere Basom, Chairman of the Annual Meeting, American Fracture Association, 520 Montana Street, El Paso, Texas.

EXPERIMENTALLY INDUCED ACUTE RESPIRATORY ILLNESS

Suspensions of pooled viruses (types 3, 4 and 7 adenovirus) grown on human intestine cells were administered parenterally to

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six volunteers of the Walter Reed Army Institute of Research. Five of the six developed an acute respiratory infection similar on all counts to pharyngo - conjunctival fever or A.R.D. conjunctivitis. All received the same dosage, but the reactions elicited were of a different degree of intensity. One volunteer, who had received three injections of killed monkey kidney adenovirus vaccine three months previously, had minimal symptoms which would have been overlooked had they not been searched for. Symptoms included conjunctival inflammation, fever, malaise, inflammation of the mucosæ of the eyes, ears, nose and throat, and lymphoid hyperplasia in the pharynx and conjunctivæ. Although no virus could be recovered from conjunctival or nasal secretions, a rapid rise occurred in the titre of neutralizing antibodies to the three viruses. This represents a difference from the naturally occurring sequence of events when such antibodies do not appear until three weeks after the disease is contracted in the usual circumstances. The experiment represents the first successful reproduction of any acute respiratory disease by the parenteral injection of such a viral etiological agent.—*J. Clin. Invest.*, 36: 1072, 1957.

PÆDIATRIC RESEARCH IN TORONTO

The Research Institute of the Hospital for Sick Children of Toronto, Canada, has recently brought out its third annual report. The present account does not expect to do justice to the numerous research projects going on in the Institute but merely hopes to bring out a few highlights.

One of the metabolic studies undertaken aimed at correlating the renal permeability to plasma proteins in different types of renal disease with sequential alterations in that permeability during various phases of renal dysfunction. The renal clearance of plasma albumin, iron-binding globulin and gamma globulin has been measured in a number of patients with nephritis, nephrosis and postural proteinuria. It has been observed that in inflammatory renal disease excretion of plasma muco-protein in the urine occurs in relatively large amounts. This phenomenon also takes place in other types of inflammatory and neoplastic diseases.

Nephrotic children have been treated with long-acting ACTH and with the more recent corticosteroids. A partial or complete remission of the disease has been induced in the majority of the patients. Follow-up treatment at home consists in administering cortisone on three consecutive days each week, progress being followed in the out-patient clinic.

The section of cardiology reported that the mortality in endocardial fibroelastosis in the past had been considered to be 100%; with prolonged use of digitalis therapy the mortality in a study group has been only 14%. The electrocardiograph in the hands of some members of this group has been perfected to the point of supplying a method of diagnosing pulmonary atresia with normal aortic root and also left coronary artery arising from pulmonary artery. In a project on rheumatic heart disease, cases treated by ACTH, cortisone and aspirin have been followed up for three years. No significant difference has been found in the results obtained with the three drugs.

The dentistry and genetics departments have been quite active in several fields of endeavour.

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Experimental studies on the healing of tendons were done in the Department of Surgery. Along the same lines 250 poliomyelitis patients who had undergone surgery for deformities were called in for investigation.

Various methods of insuring extra-corporeal circulation have been tried and some have been reported in this Journal.

NATIONAL HEART FOUNDATION OF CANADA

The first annual report of the National Heart Foundation, which was incorporated on June 1, 1956, describes its program. The primary object of its program is to establish a co-ordinated plan of research and education in cardiovascular diseases in Canada, through the co-operation of the provincial heart foundations and subsequently their local heart organizations. The Medical Executive Secretary, Dr. John B. Armstrong, has undertaken a survey of cardiovascular research support in Canada. He shows that the total in cardiovascular disease grants awarded in 1956-57 was about one million dollars, of which some $655,000 came from Federal sources, $118,000 from provincial governments and $225,000 from private agencies and donors. The Executive Secretary has also interviewed persons interested in medical research in order to obtain advice in the formulation of a research policy which would be of the greatest benefit to Canada. One result should be that persons and projects will be supported with a measure of continuity which has so far not been present.

The National Heart Foundation has begun a program of professional and lay education. It has permission to use the many excellent booklets, pamphlets, films and other materials published by the American Heart Association, Inc., and refers gratefully to the co-operation of the latter. The Foundation report shows that deaths from cardiovascular disease in Canada by 1955 amounted to 49% of all deaths, this referring to a total mortality of 62,900 out of 128,000 persons who died in Canada in that year.

The Foundation is also planning, in the interests of public relations, a program of health education at the national level and through this at the provincial and local levels. It has published a booklet entitled "The Heart Foundations of Canada" which outlines recent trends and the present status of heart disease in Canada.

IMPENDING HEPATIC COMA

When protein hydrolysate is given intravenously to patients with hepatic cirrhosis, considerable care should be taken in regulating the rate of flow so as to prevent the development of hepatic coma from a raised ammonium nitrogen

blood concentration. The recent work of members of the Second and Fourth Harvard Medical Services, Boston City Hospital, has shown that intravenous administration of amino acid solutions brought about mental confusion and flapping tremor in certain cirrhotic patients. It was noticed that a slow rate of infusion of these solutions did not produce prompt rises in blood ammonium nitrogen concentration although infusions of ammonium chloride containing the same or lesser amounts of ammonium than the hydrolysate produced prompt increases. However, if a mixture of ammonium chloride and protein hydrolysate was administered, the rise in blood ammonium nitrogen concentration did not come up to the level expected had ammonium chloride been used exclusively. Credit for this ammonium neutralization or detoxification action was given to glutamic and aspartic acids contained in the hydrolysate.— *J. Lab. & Clin. Med.*, 50: 1, 1957.

ANTIBIOTIC AGENTS IN EARLY MANAGEMENT OF WOUNDS

Although the most satisfactory prophylaxis of infection of contaminated traumatic soft tissue wounds is prompt and adequate surgical débridement, this may not be possible in times of catastrophe with large numbers of wounded to look after. The temporary prophylactic use of antibiotics or chemotherapeutic agents has not yet been fully evaluated, but Sanford and his colleagues (*Surg. Gynec. & Obst.*, 105: 5, 1957) have produced some data from studies on animals given antibiotic agents for prophylaxis of infection of contaminated soft tissue wounds. It would seem that antibiotics will never replace surgical therapy, and the experiments quoted show that they did not alone prevent the occurrence of localized wound infection in non-debrided soft tissue wounds. They did however decrease the occurrence of local extension and generalized invasive infection, and lengthened the period between wounding and the development of localized wound infection. This happened of course only when wounds had been primarily contaminated with bacteria sensitive *in vitro* to the specific antibiotic (penicillin, chloramphenicol, oxytetracycline). The delay in development of infection seems to be adequate reason for prophylactic administration of antibiotics to individuals with wounds in which primary surgical management is likely to be delayed for hours or even days. The choice of antibiotic may be aided by studies in progress to ascertain the over-all susceptibility of the bacterial mixture found in street dirt from various locations. The authors also show that exposure of rabbits to sublethal amounts of total body x-radiation did not alter the response to wounding or to the antibiotic.